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THE SYNDROME OF MALIGNANT HYPERTENSION *

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Three years ago, two of us (H. P. W. and N. M. K.) [1] reported a series of cases of characteristic retinitis associated with marked hypertension and adequate renal function. The history and clinical data differed from those usually noted in cases of chronic nephritis. We then pointed out the serious prognostic import of this typical retinitis. The term "malignant hypertension" was applied to this clinical condition, apparently correctly, because in all of the fourteen cases so diagnosed, death occurred within from one to forty-four months. Since then we have seen a large number of similar cases, in some of which moderate renal insufficiency had developed. In the present communication, we wish to present the observations in eighty-one cases. Forms of severe hypertension without this retinal picture, while recognized as potentially malignant, are not included in this series. Further data have been collected which show that this condition may occur even in childhood and that it may be superimposed on previous general arteriosclerosis and on benign hypertension. We wish to emphasize that many of these patients were up and about and generally did not complain of severe discomfort, and yet the retinal changes warned the physician of the seriousness of the general pathologic process. Detailed studies of the cardiovascular system have been made with special emphasis on the disturbances of retinal, cerebral, cardiac and renal functions. The relative impairment of the functions of these various organs differed but, when correlated, indicated the widespread effects of the disease process. In this paper, our object is to show the relationship of certain apparently isolated signs and symptoms to a definite clinical and pathologic syndrome.

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1. Wagner, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374 (Sept.) 1924.

CLINICAL SYNDROME AND PHYSICAL MANIFESTATIONS

Forty-eight of the eighty-one patients were males and thirty-three, females. The ages ranged from 9 to 64 years, the average being 42, but the majority of the patients were between 33 and 55 (fig. 1). This age incidence is similar to that reported by Fahr [2] in cases of malignant sclerosis. On examination, patients reported the onset of symptoms from one month to six years previously. These were naturally diverse; headache, general weakness and nervousness were the most common. Visual disturbances were reported in forty-three cases. Symptoms arising from actual organic lesions of the central nervous system were present in twenty-nine cases. In five cases, the history and examination

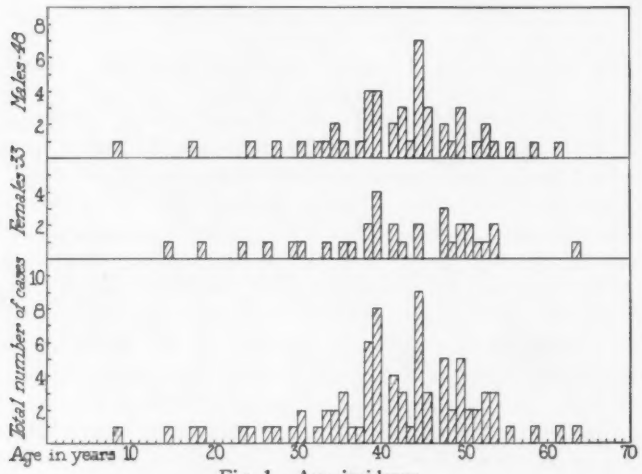

Fig. 1.—Age incidence.

suggested tumor of the brain.[3] When general convulsions occurred, the patient was usually less than 40, while hemiplegia was most common in those more than 40. Loss of weight and strength was striking in nine-

2. Fahr, T.: Nephrosclerosis, Deutsche Arch. f. klin. Med **134**:366, 1920.

3. Wagener and Woltman have found that the pressure of the cerebrospinal fluid was increased above the normal in several of these cases and that drainage by lumbar puncture temporarily relieved certain cerebral symptoms. The increased pressure of the spinal fluid in cases of hypertension has been mentioned previously by Volhard and Fahr (Die doppelseitegen hämatogen Nierenerkrankungen, Berlin, Julius Springer, 1918. Die Brightsche Nierenkrankheit, Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914. Bailliart, Magniel and Saragea (Mesures de la pression artérielle rétinienne et de la tension céphalorachidienne dans quelques cas d'hypertension artérielle, Arch. d. mal du coeur **17**: 289, 1924) and Block and Oppenheimer (A Comparative Study of Intraspinal Pressure. Blood Pressure and Intra-Ocular Tension, Arch. Neurol. & Psychiat. **11**:444 [April] 1924).

teen cases; a loss of 75 pounds (34 Kg.) in six months occurred in one case. There was a previous record of definite hypertension in forty-eight cases. This had been known to the patients for varying periods of from a few weeks to ten years. In forty-nine cases there was a history of dyspnea on exertion or of transient dependent edema. The patients rarely complained of urinary symptoms, which usually consisted of slight or moderate nocturia. In one patient who was under observation for ten years, a trace of albumin was usually present in the urine. Albumin and casts had been known to be present previously in many cases, the history in one dating back seven years. Uremic manifestations were extremely rare, and when coma occurred during the terminal picture, it was not typical of uremic states.

The general physical examination was particularly directed to the cardiovascular system. Clinical evidence of anemia was almost always absent. On account of certain symptoms of hypersensitiveness and nervousness, the thyroid gland was always palpated, but diffuse or nodular enlargements were infrequent. Evidence of paralysis was sought. Paralysis of single nerves was rare, that of the facial nerve occurring twice and of the abducens, once. Our criteria as to the extent of peripheral arteriosclerosis and sclerosis of the arterioles[4] were the appearance of the temporal and retinal arteries and the palpable condition of the radial and brachial arteries. The grade of sclerosis in the retinal arterioles, as evidenced by the degree of constriction and irregularity in caliber, varied from mild to severe. The sclerosis was marked in thirty-three cases. In nine of these, the high degree of visible sclerosis was caused in part by the associated retinitis. The amount of peripheral sclerosis varied from slight to extreme. Marked sclerosis occurred in nineteen cases. Evidence of arterial thrombosis or embolism in the limbs was not encountered. In thirty-one cases there were objective symptoms of cardiac decompensation; the symptoms were mild in twenty-two and severe in nine. Measurable cardiac enlargement was noted in many cases, although in sixteen, distinct enlargement could not be demonstrated and in forty it was slight. Extreme grades of enlargement were demonstrable in only six cases.

On auscultation, accentuation of the second aortic sound was observed in sixty-seven cases and was the most usual abnormal observation. Cardiac murmurs occurred in thirty-three cases; in twenty-one of these the murmur was systolic in time and was heard most clearly over the base of the aorta; in nine cases, an apical systolic murmur was heard; in only three was there an aortic diastolic murmur. In one case there was serious disturbance of cardiac rhythm, auricular fibrillation being present.

4. These terms are used in general throughout the paper, although it will be shown that, while varying degrees of sclerosis were found in some of the arteries, the condition in the arterioles is described more accurately by the term hypertrophy.

TABLE 1.—*Clinical Data on Admission*

Case	Age and Sex*	Date of Admission	History of Present Illness	Weight, Kg.	Size of Heart, Grade	Second Aortic Sound, Accentuation, Grade	Peripheral Sclerosis, Grade	Edema, Grade	Blood Pressure: Admission Systolic	Blood Pressure: Admission Diastolic	Blood Pressure: Dismissal Systolic	Blood Pressure: Dismissal Diastolic	Retinal Changes: Retinitis Grade	Retinal Changes: Retinitis Stage	Retinal Changes: Arteriosclerosis, Grade	Date of Death	Duration of Life From First Admission, Months	Comment
1	52 ♀	2/28/24	From 2 to 3 years; headache, dyspnea, dysarthria, visual disturbances; blood pressure: systolic 190, diastolic 90	73.6	1	2	1	1	280	160	210	135	2	3	3	1/9/25	10	
2	42 ♀	6/29/25	Headache, 4½ years; hypertension, 2 years; purpura, 1 year; visual disturbances, 2 weeks	40.0	Normal	1	3	...	265	165	240	160	2	2	2	May, 1926	11	
3	46 ♂	11/21/22 4/20/25	Albuminuria and cylindruria, 7 years; hypertension, 1 year; headache, 6 months	74.5	1 ...	1 ...	1-2 ...	... ...	220 ...	140 ...	150 ...	90 ...	1 ...	2 ...	2 2	7/29/26	44 ..	Right hemiplegia
4	50 ♀	6/19/24	Nervousness and dyspnea, 2 years; visual disturbances, 3 weeks; loss of weight	68.2	1	...	...	...	280	170	285	160	2	1	2	5/15/25	11	
5	40 ♂	9/23/21	Severe headache, 3 years; hypertension, 1 year; periodic edema of ankles	65.4	1	1	2	...	235	150	170	110	1	2	3	Jan., 1923	16	
6	53 ♀	1/31/24	Dyspnea, 9 months; dependent edema, 3 months; epistaxis, 3 weeks	91.8	1	1	1	1	240	175	205	100	2	3	3-4	12/ 4/24	10	
7	25 ♂	10/24/21	Headache; loss of vision; loss of weight for 20 months; hypertension, 18 months; epilepsy, 14 months	51.0	Normal	1	1	...	240	165	190	130	3	4	4	12/31/21	2	Question of tumor cerebri
8	45 ♂	8/26/26	Hypertension and severe headache, 5 years; visual disturbances, 1 month	57.7	1	1	2	...	230	120	200	120	1	1-2	3	1/16/27	4.5	
9	48 ♂	5/26/25	Headaches, 7 years; visual disturbances, 3 years; weakness, 2 months	75.4	1	...	3	...	235	165	210	145	2	1	2	7/ 2/25	1	
10	48 ♂	7/ 6/25	Dyspnea, 1 year; visual disturbances, 5 months	70.0	2	3	2-3	...	240	170	205	160	1	3	3	2/27/26	8	
11	40 ♀	10/ 1/24	Hypertension, 4 years; visual disturbances; slight edema; loss of weight, 10 months; dyspnea, 4months	47.0	1	1	1	...	250	160	190	120	3	3	...	March, 1925	6	
12	52 ♂	5/15/25	Hypertension, 9 years; dyspnea on exertion and headache; visual disturbances, 1 year	78.2	1	3	2-3	...	250	150	230	130	2	3	4	3/29/26	10.5	

13	39 ♂	11/ 8/26	Headache, 2½ years; hypertension and loss of weight, 2 years; visual disturbances, 2 months	70.1	Normal	1	2	...	220	140	160	120	3	2-3	1	4/ 3/27	5	
14	44 ♂	9/23/25	Headache, 2 years; visual disturbances, 1 year; dyspnea, 2 months; attacks of diplopia	75.0	2	1	3	1	240	160	225	125	3	2	2-3	Jan., 1926	4	
15	40 ♀	9/ 3/25	Headache, 1 year; loss of weight, 3 months; slight dyspnea	47.2	Normal	1	2	1	260	170	190	120	2	3-4	2	2/10/26	5	
16	37 ♀	8/19/25	Headache, dyspnea, precordial pain, and loss of weight, 1 year; visual disturbances and apoplectic stroke, 2 weeks	81.3	3	...	1+	...	240	155	208	120	2	2	3	3/22/26	7	Facial paralysis
17	30 ♀	7/29/26	Hypertension and headache, 4½ years; loss of strength 1 year	46.3	Normal	3	3	...	245	165	185	140	1	2	1	10/22/26	3	
18	24 ♀	4/27/22	Tuberculous infection of right ankle, 12 years; hypertension, 7 years; headache and visual disturbances, 2 months	58.2	Normal	2	2	...	280	190	210	140	2	2-3	2-3	3/26/23	11	
19	45 ♂	7/11/23 11/ 7/23	Hypertension and headache, 2 years; loss of weight, 1 year	75.0 66.8	1 1	1 1	2 2	... ...	195 190	130 125	175 210	120 150	1 2	1 2	2-3 2-3	2/ 8/24	7	
20	35 ♂	7/27/25	Headache and asthenia, 1 year	64.5	Normal	2	3	...	240	150	208	140	...	2	...	3/ 6/26	7	
21	40 ♂	7/23/26	Albuminuria, 7 years; attack of hematuria, 3½ years ago; hypertension and headaches, 1 year	82.7	2	2	1	...	210	120	210	150	1	2	2	8/ 8/27	12.5	
22	50 ♂	6/ 4/25	Dyspnea; asthenia; slight visual disturbances, headaches; dependent edema, 6 months	86.4	2	1	3	...	220	150	170	120	1	2	2	9/ 2/25	3	
23	50 ♀	4/19/26	Headaches; asthenia; dyspnea, 5 months; disturbance of vision, 2 weeks; metrorrhagia	60.0	1	1	2+	...	240	160	180	115	2	2	3	8/ 6/26	2.5	
24	45 ♀	1/30/26	Headache and vertigo, 2½ years; pain in back and loss of weight, 1 year	60.0	1	1	1+	1	250	130	210	100	1	2	2	Feb., 1927	12	
25	45 ♂	3/12/23	Headache, 2 years; loss of weight, 3 months; hypertension, 5 weeks	96.8	1	1	1	...	225	145	175	95	2	2	4	5/ 9/29	38	Died, "stroke"
26	46 ♂	12/16/24	Hypertension, 3 years; dyspnea and edema, 7 months; visual disturbances, 4 months	....	2-3	...	2	2	220	145	240	155	2	2-3	2	12/20/24	4†	Necropsy

* In this table and in table 4, ♂ indicates male; ♀, female.
† Days.

TABLE 1.—*Clinical Data on Admission—Continued*

Case	Age and Sex	Date of Admission	History of Present Illness	Weight, Kg.	Size of Heart, Grade	Second Aortic Sound, Accentuation, Grade	Peripheral Sclerosis, Grade	Edema, Grade	Blood Pressure: Admission Systolic	Blood Pressure: Admission Diastolic	Blood Pressure: Dismissal Systolic	Blood Pressure: Dismissal Diastolic	Retinal Changes: Retinitis Grade	Retinal Changes: Retinitis Stage	Retinal Changes: Arteriosclerosis, Grade	Date of Death	Duration of Life From First Admission, Months	Comment
27	42 ♂	12/31/25	Pain in head and hypertension, 4 years; dyspnea on exertion, 6 months; failing vision and loss of weight, 2 months	65.4	1	...	2	1	210	140	180	100	2	2	...	3/ 3/26	2	
28	31 ♀	3/ 8/24	Periodic attacks of asthenia, 4 years; marked hypertension and blindness of left eye, 4 months	45.4	Normal	3	1-2	1	270	140	200	140	2	3	3-4	8/30/24	6	
29	40 ♂	11/ 3/23	Headache and hypertension, 2 years; dyspnea, 4 months	100.4	1	1	2	...	260	160	210	150	2	3	1-2	7/ 4/24	8	
30	33 ♂	11/10/24	Loss of memory, 3 years ago for 1 month; headache with vomiting for 8 months; visual disturbances, 2 weeks	83.2	2	...	1	...	230	120	180	90	2	2	2	3/ 9/26	16	Bilateral lumbar sympathectomy
31	38 ♂	7/13/23	Headache and loss of weight and strength, and dyspnea for 1 year; hypertension, 4 months	66.0	2	3	2-3	...	255	155	230	140	2	3	1	10/15/23	3	
32	36 ♂	8/18/23	Headache; dyspnea and moderate edema, 3 years; attacks of unconsciousness, 2½ years ago	124.0	3	...	3	4	235	135	220	130	1-2	1-2	2	1/14/27	5	Necropsy
33	49 ♂	9/25/23	Severe headache and hypertension, 2 years; hemiplegia 2 years ago; slight dyspnea and edema, 2 months	63.2	2	1	3	...	215	140	210	150	1	2	1	10/27/23	1	
34	39 ♀	7/12/26	Hypertension and failing vision, 2 years; severe headache, 6 months; numbness of left hand, 3 to 4 months; dyspnea	110.0	2-3	2	1	1	200	185	240	110	3	2	3	8/29/26	1.5	
35	42 ♂	7/20/25 11/28/25	Headache and epistaxis, 1 year; dyspnea, 8 months; edema, 3 weeks	68.2	2 2-3	... ...	... 2-3	1 2	210 210	155 160	180 180	150 140	1-2 1-2	2 2	1-2 1-2	..... 2/18/26	7	
36	59 ♂	11/ 5/25 4/ 8/26	Vertigo and double vision 2 years ago; hypertension, 15 months; slight dyspnea and failing vision, 1 week	59.0	1 ...	1 ...	3 ...	... ...	250 215	150 160	200 210	130 140	2 2	1-2 3	2 3	..... 5/10/26	6	

37	45 ♀	8/26/21	Visual disturbances; vertigo; weakness; dyspnea, 8 months; hemiplegia; hypertension; loss of weight (34 Kg.), 6 months	65.0	1	1	2	1	250	140	...	...	2-3	3	2	8/31/21	5†	Necropsy
38	15 ♀	5/ 6/26	Headache, 4 years; albuminuria, 2 years; left facial paralysis, 2 months	53.6	Normal	2	2	...	200	140	170	115	2	2-3	1	4/ 4/27	11	
39	42 ♀	3/27/26	Headache and vomiting; visual disturbances, right eye; hypertension; dyspnea, 6 months	41.4	1	3	3	...	280	150	225	120	3-4	2	2	4/26/26	1	Stroke of apoplexy while in hospital
40	19 ♀	2/20/26	Headache, hypertension and periodic blurring of vision, 2 years; dyspnea and nervousness, 1 year; albuminuria, 8 months	42.3	1	3	2	...	270	150	220	150	2	3	2	4/ 7/26	1.5	Loss of weight
41	36 ♀	12/ 6/24	Headache, 6 years; severe headache, dyspnea and cardiac pain, 3 months	58.6	1	1	2+	...	225	155	200	125	2	2	2	10/19/25	11	
42	40 ♀	7/ 6/26	Failing vision, 15 months; left hemiplegia and hypertension, 8 months	63.6	4	3	1	1	204	140	220	160	2	3	2	7/31/26	25†	
43	35 ♂	1/27/25	Hypertension, 6 years; visual disturbances and albuminuria, 10 months; pulmonary edema, 1 month ago	84.1	3	2	2	...	240	165	230	130	3	3	...	Summer, 1925	6	
44	39 ♂	8/17/26	Headache, 2 years; vertigo; dyspnea; visual disturbances left eye, 1 year; hypertension; numbness of left side 10 months	68.2	1-2	2	3	...	240	155	210	140	3-4	2-3	2-3			
45	45 ♂	7/21/25	Headache, hypertension and nervousness 3 years; dyspnea and edema of ankles, 3 to 4 months	74.1	1	1	2	...	220	150	165	110	1	3	3	3/ 9/26	8	Necropsy, examination of kidneys only
46	28 ♂	5/14/25 8/ 7/25	Dyspnea, tachycardia and trace of edema, 1 month	96.4 91.8	... 3	... 3	... 2+	... 1	230 220	160 180	175 195	120 150	2 2	2 3	2 2	 1/22/26	 8	
47	53 ♂	3/14/25 2/24/26	Insomnia and dyspnea, 2½ years; right hemiplegia; headache; vertigo; hypertension; edema of ankles, 18 months; loss of weight	84.1	1-2 ...	... 3	2-3 3	1 ...	220 220	140 140	190 220	110 140	1 2-3	1 3	3 3	 4/ 2/26	 12.5	 Pulmonary edema in hospital
48	64 ♀	2/ 3/25	Headache; vertigo; right hemiplegia; dyspnea; edema of legs 1 year; visual disturbances, 6 months	60.5	2	...	2	...	260	190	180	100	2	3-4	4			
49	36 ♂	6/ 3/24	Hypertension, 5 years; albuminuria; cylindruria, 3 months; headache, constant, 3 weeks	66.8	1-2	2	3	...	245	145	230	130	2	2	3	7/19/24	1.5	Hematuria in hospital
50	54 ♀	6/ 2/25	Hypertension, headache and vertigo, 3 years; attack of unconsciousness 6 months ago	58.6	1	1	2	...	240	140	230	130	2	3	2	11/16/25	5.5	

TABLE 1.—*Clinical Data on Admission—Continued*

Case	Age and Sex	Date of Admission	History of Present Illness	Weight, Kg.	Size of Heart, Grade	Second Aortic Sound, Accentuation, Grade	Peripheral Sclerosis, Grade	Edema, Grade	Blood Pressure: Admission Systolic	Admission Diastolic	Dismissal Systolic	Dismissal Diastolic	Retinal Changes: Retinitis Grade	Retinitis Stage	Arteriosclerosis, Grade	Date of Death	Duration of Life From First Admission, Months	Comment
51	34 ♀	6/10/25	Headache and asthenia, 8 months; dyspnea and edema of ankles, 5 months	56.8	1	3	2	1	240	160	240	150	3	3	3	Sept., 1925	3	
52	45 ♂	7/15/26	Headache, 7 years; hypertension, 1 year; loss of weight and dyspnea, 6 to 8 months	72.3	1	2	2	...	240	180	220	160	2	2	3	12/ 5/26	4.5	
53	56 ♂	8/ 9/22	Hypertension, 4 years; no subjective complaint; memory failing, 2 to 3 years; dyspnea with two attacks of pulmonary edema in last 6 months	66.4	1	...	2	...	190	110	170	115	1	1	3			
		5/10/26		61.4	1	2	3+	...	210	160	235	155	2	2	3	6/24/26	51	
54	59 ♂	12/ 2/24	Dyspnea on exertion, 5 years; hypertension; headache; vertigo with vomiting and visual disturbances, 4 years	101.4	2-3	1	2+	2	230	135	180	100	1	2	3	11/20/25	12	Orthopnea and attack of pulmonary edema in hospital
55	43 ♀	4/ 8/25	Headache and hypertension, 7 years; dyspnea and edema of feet, 4 years; orthopnea and dependent edema, 5 months;	92.3	2	2	2	1-2	280	150	220	125	2	3	2			
		7/20/25	Persistent dyspnea and dependent edema	89.5	2	2	2	2	245	190	260	180	2	3	2	9/ 6/25	5	
56	45 ♂	1/25/26	Subconjunctival hemorrhage; diplopia; blurred vision, 2 months; headache, 2 weeks	55.0	Normal	3	3	...	160	100	190	110	1	1	2	3/20/26	2	
57	48 ♀	12/18/24	Metrorrhagia, 4 years; dyspnea and edema of ankles, 1 year	87.3	1	1	1	1	205	125	170	95	1	2	3	1/ 6/27	24.5	"Stroke," Sept., 1926
58	34 ♂	1/ 2/26	Headache; weakness and loss of weight, 2 years; attack of unconsciousness 5 months ago	70.0	1	2	2+	...	245	100	195	140	2	3	2	3/23/27	15	Essential hematuria; cystoscopic examination
59	27 ♀	9/25/24	Intermittent attacks of hematuria, 6 years; hypertension and headache, 16 months	58.6	1	3	1—	...	260	140	230	135	2	3	2			

60	9 ♂	7/ 3/26	Periodic attacks of headache and projectile vomiting, 5 years; nine convulsions 5 months ago	25.0	Normal	...	1	...	190	130	180	130	1-2	3	1	.....	..	Question of tumor cerebri
61	48 ♀	3/10/24	Headache and vertigo, 10 years; dyspnea, 6 years; hypertension, 2 months	70.0	1	2	2	...	210	140	215	110	1	3	2-3			
		2/28/25		71.0	...	...	...	...	210	110	200	100	1	4	2-3			
62	50 ♂	6/25/26	Headache; asthenia; vertigo; hypertension, 6 years; dyspnea; edema of feet; visual disturbances, 6 months	49.1	Normal	2	3	1	210	150	200	110	3	2-3	4	8/25/26	2	Periodic respiration in hospital
63	51 ♀	9/16/26	Dyspnea on exertion; headache; hypertension, 8 months; orthopnea, 6 months; dimness of vision, 1 month	58.6	1	1	1+	1	250	160	250	125	3	2	2	10/16/26	1	
64	39 ♀	9/17/25	Occipital headache, 2 years; vertigo; asthenia; dyspnea, 7 months	72.3	1	...	1—	...	240	120	170	100	2	3	3			
		3/17/26	General health improved....	68.6	...	...	...	...	215	140	185	125	2	3	3			
65	46 ♂	6/ 4/25	Hypertension; nervousness; occipital headaches 3 years; visual disturbances in right eye, 5 weeks	82.7	2	1	1	...	240	145	230	130	2	2-3	3			
		7/15/26	Headaches more frequent...	....	2	1	1-2	...	240	150	245	160	2	3	3			
		9/ 5/26	Nausea and vomiting, last 3 weeks	....	...	...	...	...	220	140	185	110	2	3	3	10/ 4/26	16	Attacks of pulmonary edema; died in hospital
66	54 ♀	12/ 6/23	Dyspnea and asthenia, 5 years; attack of dyspnea and edema of legs 10 months ago; recurrence of dyspnea 2 weeks ago	99.5	1	2	1	1	210	160	210	130	3	2	2			
		9/14/24	Visual disturbances 3 months	....	3	3	2	3	200	140	...	...	3	3	2	9/19/24	9.5	Necropsy
67	43 ♂	10/15/26	Dyspnea, weakness and nervousness, 18 months; edema of legs 1 year; hypertension known for 6 months	86.4	2	1	2	1—	255	155	240	150	2	3	3-4	2/ 6/27	8.5	
68	48 ♀	7/10/25	Headache, 4 to 5 years; severe headache, 1 year; diplopia, 1 week	58.2	1	3	1-2	...	275	150	255	140	2	2-3	3	.....	15.5	Paralysis external rectus of left eye
		7/27/26	Severe headaches, 4 months	56.8	1	...	2	...	280	160	250	140	2	3	3	10/26/26		
69	49 ♀	4/ 4/23	Hypertension for 10 to 13 years; headaches for many years; visual disturbances; vertigo; edema of ankles, 9 months	82.3	1	1	2	...	220	105	170	100	2	2-3	2-3			
		2/ 6/25	Attacks of numbness left arm and leg; dysarthria	75.5	2	1	2	...	260	120	200	120	2	2-3	2-3			
		5/21/26	.....	66.7	2	1	2-3	1—	170	100	210	125	2	3	3	12/ 8/26	44	Died; apoplectic stroke
70	53 ♂	4/22/26	Headache, dizziness and hypertension, 2 years; failing vision, 18 months; loss of weight, 10 months	49.5	1	2	4	...	250	170	230	155	4	3	3-4	6/10/26	1.5	

TABLE 1.—*Clinical Data on Admission—Continued*

Case	Age and Sex	Date of Admission	History of Present Illness	Weight, Kg.	Size of Heart, Grade	Second Aortic Sound, Accentuation, Grade	Peripheral Sclerosis, Grade	Edema, Grade	Blood Pressure: Admission, Systolic	Blood Pressure: Admission, Diastolic	Blood Pressure: Dismissal, Systolic	Blood Pressure: Dismissal, Diastolic	Retinal Changes: Retinitis, Grade	Retinal Changes: Retinitis, Stage	Retinal Changes: Arteriosclerosis, Grade	Date of Death	Duration of Life From First Admission, Months	Comment
71	51 ♀	1/ 2/25	Hypertension and dyspnea, 6 years; weakness; dimness of vision; loss of weight, 1 year	70.0	2	1	1-2	1—	270	160	210	170	3	2-3	2	8/ 7/25	7	
72	40 ♀	7/10/25	Miscarriage, 16 months ago; since then headache, weakness and loss of weight	64.5	1	3	1—	1—	250	180	210	165	2	3	2	9/ 1/25	2	Right hemiplegia in hospital
73	31 ♂	4/18/21	Headache, 2 to 3 years; dimness of vision, 6 months; epileptiform convulsions 6 weeks ago	56.8	Normal	1	1	...	260	160	225	155	3	3	3	7/ 8/21	2.5	Question of tumor cerebri
74	43 ♂	9/19/24	Hypertension and headaches, 3½ years; dyspnea, 6 months; blurred vision, 1 month	61.0	1	...	2	...	250	160	220	130	2	2-3	3	2/28/25	5.5	
75	54 ♂	7/22/24	Attack of frontal headaches; vertigo; vomiting; right hemianopia 8 months ago; vertigo and aphasia since	85.0	Normal	3	3	...	215	130	160	100	2	3	3	10/31/24	3	
76	18 ♂	8/13/26	Periodic severe headache, 3 years; convulsions; blurred vision; albuminuria, 6 months	52.3	Normal	1	1-2	...	240	180	220	140	3	3	4	.....	..	Question of tumor cerebri
77	45 ♂	11/ 1/23	Hypertension and albuminuria, 5 years; headache, 1 year; insomnia and loss of weight, 7 months	75.9	2	2	2	...	250	190	190	145	3	2-3	2-3	12/25/23	2	
78	39 ♂	2/ 6/23	Headache, 3 years; severe headache, hypertension and loss of weight, 1 year	64.1	1	1	2	...	250	175	195	115	4	...	3	7/28/23	6	Lost 45 pounds in last year
79	40 ♂	12/21/20	Nocturia, 1 year; failing vision, 7 months	50.4	1	...	2-3	...	240	160	225	140	4	3	...	1/29/21	1	Convulsion in hospital; question of tumor cerebri
80	62 ♂	8/11/25	Headaches for 6 years; hypertension; loss of memory; dyspnea; asthenia; failing vision, 7 months; loss of weight	....	2	...	3	...	240	120	200	100	2	3	3	8/19/25	8†	Necropsy
81	50 ♂	1/27/27	Dyspnea, 1 year; marked dyspnea, 4 months; marked edema, 2 weeks; general convulsions in hospital	95.5	3	1	2	3	220	140	225	130	2	1-2	2	3/ 7/27	1	Necropsy

At the time of examination, only one case did not show distinctly high blood pressure. The patient was asthenic. The systolic blood pressure on admission was 160 and the diastolic, 100. After a stay in the hospital the patient gained in weight and the blood pressure rose to 190 systolic and 110 diastolic. In eighty cases the maximal systolic reading varied from 220 to 280 and the diastolic from 120 to 190.

With one exception, retinitis was present in all cases at every examination. In one case, a typical but mild retinitis observed at the first examination completely subsided while the patient was under observation. In the series the retinitis varied in grade from mild, with only slight papilledema and a few exudates and areas of hemorrhage, to severe, with as much as 6 diopters swelling of the optic disk, extensive edema of the retina, and many areas of hemorrhage and exudates of various types. In more than half of the cases, the retinitis was of moderate severity with papilledema of less than 2 diopters. In ten cases, the swelling of the disks measured 3 or more diopters. While forty-three of the patients complained of blurred vision, central vision was definitely reduced objectively in only half that number. The impairment of vision seems to be associated with the spread of the edema into the macular region in the second stage of the retinitis. In three cases, there was a definite unilateral central scotoma associated with edema in the macular region. With recession of the edema and the appearance of a partial macular star, the scotoma disappeared. In one case right homonymous hemianopia, apparently due to a cerebral vascular accident but not associated with hemiplegia, was present. In one case, vision in one eye was reduced to perception of light by extensive hemorrhage into the vitreous. In most cases the vision was surprisingly good. Detailed data are incorporated in table 1.

LABORATORY TESTS

Certain laboratory tests were usually carried out as a routine. The results are detailed in table 2. The absence of anemia suspected from the examination of the mucous membranes was confirmed in sixty-six cases. If anemia was present, there was usually a history of bleeding. Epistaxis occurred in two cases, petechiae in two, uterine bleeding in two, hematuria in five and in two cases, profuse bleeding followed tonsillectomy. In one case in which anemia was present, therapeutic phlebotomy had recently been performed twice. Hemoglobin was determined by the Dare, carbon monoxide and acid-hematin [5] methods. Thus, the absence of clinical signs of anemia and negative laboratory evidence

5. Osgoode, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107, 1923. Palmer, W. W.: The Colorimetric Determination of Hemoglobin, J. Biol. Chem. **33**:119, 1918.

TABLE 2.—*Laboratory Data on Admission*

Case	Electrocardiogram, Leads I, II, III	Basal Metabolic Rate	Blood*						Urine								
			Erythrocytes, Millions	Hemoglobin, Per Cent (Dare)	Hemoglobin, Acid Hematin or Carbon Monoxide, Gm. per Cent	Urea, Mg. per Cent	Creatinine, Mg. per Cent	Uric Acid, Mg. per Cent	Specific Gravity: Variation	Specific Gravity: With Concentration Test	Specific Gravity: With Water Test	Albumin, Grade	Casts, Grade	Phenolsulphonphthalein, per Cent	Chloride Test, Percentage Concentration†: Before Injection	Chloride Test, Percentage Concentration†: After Injection	Output After Water, Cc.	Urea Index
1	Normal	+11	5.14	85	....	28	1.8	...	1.005-1.030	1.030	1.005	0-1	Rare hyaline	60	...	...	1,350	..
2	Normal	+17 +13	4.90	78	14.2	28-36	1.3	2.4	1.000-1.020	1.020	1.000	0-1	.....	40	...	...	1,345	..
3	Normal, second admission	....	4.60	76	....	32	...	3.2	1.001-1.031	1.028	1.001	0-1	0-1	55	...	...	1,005	..
4	Normal	+22 +27	....	88	....	30	1.8	...	1.010-1.025	.....	.....	1-2	1	60	...	...	.....	..
5	Inverted T wave in I	+11 +11	4.60	76	....	29	1.6	3.1‡	1.001-1.027	1.027	1.001	1-3	1-3	60	...	...	1,145	..
6	Premature contractions	+27 +31	4.30	72	14.2	13-28	1.4-1.6	2.8-3.0	1.002-1.021	1.021	1.002	0-2	Hyaline 1-2	60	...	...	.....	..
7	Inverted T wave in I	+ 7	4.70	78	....	27	1.4	3.6‡	1.006-1.034	1.034	.....	1	Occasional	65	...	...	.....	..
8	.....	....	4.60	68	....	18-37	1.3	...	1.000-1.024	1.024	1.000	0-1	.....	50	...	...	1,625	..
9	Inverted T wave in all leads	....	4.20	70	14.1	45-48	2.0	4.0	1.010-1.013	.....	.....	0-2	Rare hyaline	35	...	...	.....	..
10	Inverted T wave in all leads	....	3.60	70	13.7	30-35	1.7	4.8-5.1	1.002-1.020	1.020	1.002	0-1	Occasional	50	...	...	.....	..
11	Inverted T wave in I and II	....	4.20	73	15.4	20-26	1.5	2.4-3.7	1.000-1.013	1.013	1.000	1	.....	55	...	...	860	..
12	Inverted T wave in I and II	....	4.40	72	13.6	27	1.1	3.2	1.016-1.021	.....	.....	0-2	Occasional	50	...	...	.....	..
13	Normal	....	4.26	78	....	15	1.8	...	1.000-1.020	1.020	1.000	1	.....	55	...	...	1,550	..
14	Inverted T wave in I and II	+27	3.77	74	11.5	24-34	1.0	...	1.005-1.016	.....	.....	1-2	Occasional	20-30	...	...	.....	..
15	Normal	+10	4.40	71	12.2	39	1.5	...	1.005-1.020	1.020	1.005	1-2	Occasional	35-40	...	...	.....	..
16	Inverted T wave in all leads	+27	4.30	79	14.5	22	1.3	...	1.010-1.025	.....	.....	0-1	Rare	70	...	...	.....	..
17	Inverted T wave in I, slurred Q R S in I	....	4.96	78	14.8	17-40	1.8	...	1.009-1.022	1.022	.....	0-2	Rare	50-75	...	...	.....	..
18	Normal	+13 +18	4.60	76	15.5	18	...	...	1.009-1.024	.....	.....	1-3	.....	45	...	...	.....	..
19	.....	+11	4.60	75	....	22	...	...	1.018	.....	.....	...	1	35	...	...	.....	..
20	.....	....	4.36	70	12.2	24-35	1.6-1.7	3.6	1.000-1.018	1.014	1.000	1-3	1	40	...	...	.....	..
21	Normal	— 1	5.10	86	....	17-32	1.8-2.1	...	1.000-1.019	1.019	1.000	0-2	.....	55	...	...	1,325-1,405	26
22	Normal	....	4.03	75	14.6	36-50	1.8	3.8	1.006-1.025	1.025	.....	1-3	1	30	...	...	.....	..
23	Inverted T wave in I	....	3.50	58	....	28-42	1.4	...	1.002-1.025	1.025	1.002	0-1	.....	40-45	...	...	1,115	..
24	Inverted T wave in I and II	....	4.00	70	....	29-31	1.8	...	1.002-1.026	1.018	1.002	1	Rare	40	...	...	1,600	..
25	Normal	+23 +28	4.70	78	14.0	22-32	1.7	3.7	1.002-1.027	1.027	1.002	0-1	1	65	0.8	1.4	1,110	..
26	Q R S notched	+ 8	....	..	....	99-115	3.6-4.1	4.6	1.015-1.020	.....	.....	1-2	1	20	...	...	.....	..
27	Inverted T wave in I and II	....	4.17	68	14.2	46-62	1.7-2.2	...	1.001-1.022	1.022	1.001	1-2	1	40	...	...	.....	..
28	Normal	+14	4.60	75	15.5	18-20	1.8	1.7	1.005-1.023	.....	.....	0-2	Rare	60-80	0.6	1.0	.....	..
29	.....	+14	....	..	17.8	37	2.3	5.1	1.003-1.026	.....	1.003	1-2	1-3	..	1.3	3.2	.....	..
30	Normal	....	4.20	73	17.0	16-20	1.6	4.0	1.005-1.030	1.024	1.005	0-1	Occasional	50-70	0.7	1.2	1,355	..
31	Inverted T wave in I and II	+15	....	..	16.0	29	1.8	4.0	1.001-1.030	1.030	.....	1-2	.....	40	...	...	.....	..
32	.....	....	5.44	81	16.8	52-83	3.3-5.3	...	1.004-1.019	.....	.....	0-2	1	10-20	...	...	.....	..
33	Inverted T wave in I and II	....	....	..	16.5	29	2.3	3.6	1.005-1.025	1.025	.....	1-2	1	55	...	...	.....	..
34	Inverted T wave in II and III	+18 +17 +21	4.70	72	....	47-66	2.2-3.2	...	1.003-1.013	1.012	1.003	1-2	.....	25	...	...	.....	..
35	Normal	....	5.22	84	19.3	15	1.3	4.2	1.010-1.021	1.021	.....	0-2	1	50	...	...	.....	..
36	Normal	— 8	3.83 4.36	70 75	13.8	30-34	1.7	...	1.010-1.020	.....	.....	1	2	40	...	...	.....	..

37	.....	....	5.10	82	....	34	1.9	...	1.006-1.026	.....	1.000	1	Occasional	..	...	...	905	..
38	Normal.....	....	4.63	80	....	27	...	...	1.000-1.026	1.026	1.001	1-2	.....	55-70	...	...	1,270	..
39	.....	+11	4.42	76	....	48	...	...	1.011-1.015	.....	.....	1-2	.....	35	...	...	.....	..
40	Normal.....	+20 +13 + 5	4.91	75	....	23-32	1.6	...	1.006-1.027	1.027	1.000	1-3	1	45	...	...	.....	..
41	Normal.....	+ 5	4.50	73	12.9	10-24	1.4	2.4	1.000-1.025	1.018	1.000	1	Rare	40-55	0.8	1.1	1,075	..
42	Notched Q R S in I and III....	....	4.86	82	....	29	2.0	...	1.006-1.016	1.016	1.000	1	.....	40	...	...	.....	..
43	Inverted T wave and slurred Q R S in I and II	+18 +20	4.20	79	11.5	27	1.6	3.3	1.006-1.016	.....	1.000	1	.....	40	...	...	540	..
44	Inverted T wave in I and II...	....	5.04	76	18.3	19-35	1.5-1.7	...	1.001-1.020	1.020	1.001	1	.....	60	...	...	620	..
45	Normal.....	....	3.80	75	15.2	32-36	1.8	3.2	1.001-1.015	1.015	1.001	1	.....	55	...	...	1,180	..
46	Inverted T wave in I and II...	....	4.72	82	....	30-36	...	...	1.005-1.026	1.026	1.005	1-2	Occasional	..	...	...	.....	..
47	Inverted T wave in all leads...	....	4.20	73	....	33-40	2.0	...	1.001-1.023	.....	1.001	1-2	Rare	30	...	...	975	..
48	Inverted T wave in I.....	+ 9	4.50	73	....	23	1.7	...	1.001-1.020	1.017	1.001	Tr.	.....	45	...	...	1,770	..
49	Inverted T wave in all leads...	+22 +28	4.70	71	17.9	10-36	1.5	2.9	1.001-1.020	1.020	1.001	1-2	1	60	...	...	505-565	..
50	Inverted T wave in II and III.	....	4.30	73	15.1	22	1.2	2.6	1.001-1.020	1.020	1.001	Tr.	.....	40	...	...	760	..
51	Inverted T wave in I.....	....	4.32	70	12.0	25-33	1.8-2.0	...	1.003-1.025	1.025	1.003	Tr.	Rare	45	...	...	.....	..
52	Inverted T wave in all leads...	+ 6	4.80	75	....	38-39	...	...	1.000-1.018	1.018	1.000	1-2	1	35-45	...	...	1,360	18
53	Normal.....	....	....	75	....	26	...	...	1.003-1.030	1.030	1.003	1	Rare	45-55	...	...	710	..
54	Auricular fibrillation, inverted T wave in I	+26	4.50	76	14.5	17-53	1.9-2.1	2.2-5.1	1.014-1.025	.....	.....	1-2	Occasional	50	...	...	.....	..
55	Inverted T wave in all leads...	....	4.00	70	14.8	24-35	1.6	3.8	1.010-1.030	.....	.....	1-2	Rare	40	...	...	.....	..
56	Inverted T wave in I.....	....	4.72	77	13.5	70-102	2.3-5.0	...	1.004-1.016	.....	1.004	1-2	Rare	25-30	...	...	525	..
57	Inverted T wave in I.....	+ 7	4.52	65	11.1	15-36	1.3	3.5	1.010-1.025	1.025	.....	1-2	.....	50	...	...	.....	..
58	Inverted T wave in I and II...	....	4.30	78	....	23-26	1.3	...	1.002-1.021	1.021	1.002	1-2	Rare	45	...	...	1,275	..
59	Inverted T wave in I and II...	....	4.33	75	12.8	18-34	1.5	3.4	1.000-1.020	1.020	1.000	1	.....	50-55	...	...	1,275	..
60	.....	....	4.72	80	....	18-19	1.7	...	.....	.....	.....	Tr.	.....	80	...	...	.....	..
61	Inverted T wave in I and II...	....	4.46	72	13.6	26-34	1.4-1.6	3.5-4.5	1.002-1.024	1.024	1.002	1	1	45	...	...	1,375	..
62	Inverted T wave in I and II...	+ 3	5.20	77	....	32-48	2.3	...	1.002-1.018	.....	.....	1-2	.....	45	...	...	.....	..
63	Inverted T wave in I and II...	....	3.68	61	....	82-115	3.4-4.4	...	1.005-1.010	.....	.....	1-2	.....	10	...	...	.....	..
64	Inverted T wave in I and II...	+15	4.18	77	12.3	16-19	1.1	...	1.010-1.022	.....	.....	1	.....	80	...	...	.....	..
65	Inverted T wave in I.....	+ 7	4.00	71	....	28-34	1.4	3.4	1.003-1.025	1.025	1.003	1	Occasional	45	...	...	1,055	..
66	Normal.....	....	4.71	75	....	33	1.8	...	1.009-1.018	.....	.....	1-2	Rare	40	...	...	.....	..
67	Inverted T wave in I, slurred Q R S in I and II	....	4.36	70	....	32-41	2.0	...	1.013-1.020	.....	.....	1-2	.....	45	...	...	.....	..
68	Inverted T wave in I.....	....	4.20	80	15.0	18	1.9	3.3	1.000-1.025	1.020	1.000	0-Tr.	Rare	60	...	...	1,325	..
69	Inverted T wave in II and III.	+11	4.10	76	14.8	22-24	1.6	3.2	1.010-1.029	1.024	.....	0-Tr.	.....	55	...	...	.....	..
70	Inverted T wave in all leads...	....	3.78	67	13.8	28-53	2.4	...	1.003-1.012	.....	1.003	0-1	.....	25	...	...	1,145	..
71	Inverted T wave in I.....	+17	3.52	70	14.0	11	1.5	2.6	1.003-1.016	.....	.....	1	.....	40	...	...	900	..
72	Inverted T wave in I.....	....	4.20	72	....	23-134	2.1	3.7	1.000-1.016	1.016	1.000	1-2	1	35-40	...	...	1,110	..
73	.....	+14	4.46	74	....	35-46	1.5	2.7-3.4‡	1.003-1.030	1.027	1.003	1-2	1-2	70	...	...	1,090	..
74	Inverted T wave in all leads...	+ 9	4.60	72	16.2	22-38	1.6	2.6-3.3	1.002-1.023	1.023	1.002	1	Occasional	35-50	...	...	865	..
75	Normal.....	— 7	4.21	83	14.4	38-39	1.8-1.9	2.4-2.6	1.000-1.022	1.022	1.000	1	1	55	...	...	1,575	..
76	Normal.....	+12	4.74	78	15.9	14-23	1.7	...	1.000-1.020	1.020	1.000	0-2	Rare	50-75	...	...	750	58
77	Normal.....	+40 +32	4.60	75	....	32	2.0	4.4	1.001-1.020	1.020	1.001	1-2	1	45	0.7	1.5	1,030	..
78	Inverted T wave in I and II...	....	4.90	79	14.0	25-55	2.4-2.7	3.3-4.5	1.009-1.015	1.014	.....	1-2	1	35	0.3	0.1	.....	..
79	.....	....	4.60	60	....	34-42	1.6	1.9-2.9‡	1.004-1.016	.....	.....	1-3	1-3	40	...	...	.....	..
80	Normal.....	....	4.62	87	15.0	49-101	2.0-4.5	...	1.012-1.018	.....	.....	1	Occasional	..	...	...	.....	..
81	Auricular premature contraction, inverted T wave and slurring of Q R S in all leads	....	3.50	62	....	88-144	4.3-7.1	...	1.006-1.020	.....	.....	1-2	.....	..	...	...	.....	..

* The Wassermann reaction with the blood was negative in the seventy-five cases tested, except in case 64; in cases 7, 28, 58 and 79, the Wassermann reaction on the spinal fluid was negative.

† Normal before injection, from 0.8 to 1.9; after injection, from 1.8 to 2.0

‡ Blood uric acid; Folin and Wu method (J. Biol. Chem. **38**: 81, 1919).

were in striking contrast to what one usually sees in advanced cases of chronic glomerulonephritis. A definite history of the characteristic manifestations of syphilis was not obtained in any case. The Wassermann test was carried out in seventy-five of the eighty-one cases. In only one of these was it positive, although in a second case the patient's physician had reported a previous positive reaction and had instigated immediate intensive treatment. Of the five cases in which the test was not carried out, in one, necropsy did not reveal distinct evidence of syphilitic involvement. The Wassermann test was also negative in the spinal fluid in four cases. Such evidence indicates that syphilis is not important etiologically in the malignant form of hypertension.

Electrocardiographic tracings were taken in seventy cases. Auricular fibrillation occurred in a single case and slurring of the Q. R. S. waves was present in three cases. The only other abnormality encountered was inversion of the T wave. Significant inversion occurred in forty-four cases. In two cases the T waves became negative between the first and second admission. Thirty of these forty-four patients died within a year, confirming Willius' observation [6] of the prognostic significance of inversion of the T wave (table 3). However, one must note that inversion of the T wave was not found in twenty cases in which death occurred within a period of one year. It is of interest that in ten cases in which the T wave was inverted in all three leads, obvious cardiac decompensation occurred in only three. The capillaries of the nail-fold were observed by G. E. Brown, according to the Lombard technic, in twenty-one cases. It soon became evident that abnormalities in the capillary blood flow occurred in many of these cases, and this was, in rare instances, accompanied by structural changes in the capillaries themselves, the most important of which was the definite tortuosity and contraction of the loops. The most notable change in blood flow was to the fast, intermittent or spurting type. This was noticeable in half of the cases (table 4).

The extent of the renal injury was estimated by: (1) the presence or absence of albuminuria and, when present, the amount; (2) the presence or absence of cylindruria and, when present, the grade; (3) the excretion of phenolsulphonphthalein; (4) the water output after the water test of Volhard and Fahr;[7] (5) the range of specific gravity

6. Willius, F. A.: Observations of Negativity of the Final Ventricular T Wave of the Electrocardiogram, Am. J. M. Sc. **160**:844, 1920; Electrocardiography and Prognosis: I. Significant T Wave Negativity in Isolated and Combined Derivations of the Electrocardiogram, Arch. Int. Med. **30**:434 (Oct.) 1922.

7. Volhard, Franz: Die doppelseitigen hämatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1918. Volhard, Franz, and Fahr, K. T.: Die Brightsche Nierenkrankheit; Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

following the water test and concentration test of Volhard and Fahr; (6) the determination of the concentration of urea in the blood; (7) the estimation of the concentration of creatinine in the blood; (8) the estimation of the concentration of uric acid in the blood; (9) the chloride excretion during a control period and after intravenous injection of 10 per cent sodium chloride solution; (10) the sodium benzoate test of Kingsbury and Swanson [8] and (11) the urea index, as advocated by Van Slyke.[9] The application of tests 9, 10 and 11 was limited to a few cases.

Albumin was graded from 0 to 3; cylindruria was often absent and was present up to grade 4. From the standpoint of excretory efficiency of the kidney, renal function was estimated on the basis of the output of phenolsulphonphthalein, the variation in the specific gravity of the urine, the amount of water excreted under given conditions and the concentration in the blood of urea, creatinine and uric acid. On the basis of the foregoing tests, our cases at the time of initial examination fall into four

TABLE 3.—*Electrocardiograms with Alterations in the T Wave*

	Cases
T wave inverted in lead I	14
T wave inverted in leads I and II	18
T wave inverted in leads II and III	2
T wave inverted in leads I, II and III	10

groups; normal and mild, moderate and severe renal insufficiency. In twenty-one cases renal function was comparatively normal; in forty-six, insufficiency was mild, in seven, it was moderate and in seven, it was severe. Of the cases in which it was severe, definite cardiac decompensation was present in three (table 5). In two cases there was decreased specific gravity, associated with a high output of water (1,575 to 1,770 cc.), a condition of hyposthenuria. In four other cases, decreased specific gravity accompanied a good output. In two cases in which the concentration was low, the water output was markedly reduced (from 500 to 620 cc.). In five cases, there was a similar decrease in specific gravity with moderately reduced output. In seven cases in which the sodium chloride test was carried out, six showed normal or slightly reduced concentration while one showed markedly diminished output. The sodium benzoate test was carried out in a single case, and a normal result was obtained. The urea index of Van Slyke [9] was determined in

8. Kingsbury, F. B., and Swanson, W. W.: The Synthesis and Elimination of Hippuric Acid in Nephritis: A New Renal Function Test, Arch. Int. Med. **28**:220 (Aug.) 1921.

9. Van Slyke, D. D.: Urea Index Formula, personal communication to the authors. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211, 1914.

TABLE 4.—*Studies on the Cardiovascular System*

Case	Age	Sex	Blood Pressure on Admission		Enlargement of Heart on	Peripheral Sclerosis on	Retinal Sclerosis by	Capillaries of the Nail-Folds								Significant Changes in Capillaries
								Morphologic Changes			Functional Changes in Flow					
											Uniform		Intermittent			
			Systolic	Diastolic	Percussion, Grade	Palpation, Grade	Ophthalmoscope, Grade	Straight Loops	Tortuosity of Loops	Contraction of Loops	Fast	Slow	Fast	Slow	Interrupted	
1	52	♀	280	160	1	1	3*	..	+	+++	..	..	++	..	..	Definite disturbance in flow; tortuosity and contraction excessive for age
3	46	♂	220	140	1	1-2	1	..	+	++	++	..	++	..	..	Contraction marked for age; normal fast flow
5	40	♂	235	150	1	1-2	2	..	++	++	..	++	..	..	..	Changes moderately marked for age; definite disturbance in flow, spastic type
6	53	♀	240	175	1	1	3-4*	..	..	+++	++	..	+	..	..	Marked contraction for age; mild disturbance in flow
7	25	♂	210	165	Normal	1	4*	..	+	+	++	..	+	..	..	Very slight changes in form and flow
17	30	♀	215	165	Normal	3	1	+	..	..	..	..	..	..	..	Normal appearance and flow
18	24	♀	280	190	1	2	2	..	..	++	..	++	..	++	..	Mild changes in form; marked disturbance in flow
28	31	♀	270	140	1	1-2	3-4*	..	++	+++	..	..	+++	..	..	Contraction and tortuosity out of proportion to age; marked disturbance in flow
30	33	♂	230	120	2	1	2	+	..	++	..	..	++	..	..	Mild contraction and mild disturbances in flow
31	38	♂	255	155	2	2-3	1	..	..	+++	..	..	..	..	..	Contraction excessive; decreased number of open capillaries
32	36	♂	210	130	2	...	1	..	..	++++	..	..	+++	..	..	Changes in form excessive; retarded flow observed in cardiac decompensation
38	15	♀	200	138	Normal	2	1—	..	..	+	..	..	..	..	+	No changes in form; disturbance in flow limited to isolated capillaries
44	39	♂	240	155	1	3	2-3	+	..	+++	..	..	+++	..	..	Contraction and disturbance in flow distinctly abnormal
59	27	♀	250	140	1	1—	2*	..	++	+++	..	..	+++	..	+	Excessive contraction and accelerated flow
60	9	♂	190	130	Normal	1	1—	..	..	++	..	..	+++	..	..	Marked disturbance in flow
61	48	♀	210	140	1	2	2-3*	..	+++	+++	..	..	+++	..	++	Changes in form marked; flow abnormal
71	51	♀	270	160	2	1-2	2*	..	..	++	..	..	+++	..	++	Flow probably abnormal
74	43	♂	250	160	1	2	3	++	..	++	..	..	++	..	+	Marked lengthening and moderate contraction of loops; mild disturbance of flow
76	18	♂	240	180	1	1-2	4*	..	..	+++	..	..	..	..	..	A few loops showed marked contractions; definite disturbance in flow
77	45	♂	250	190	2	2	2-3*	..	++	+++	++	..	..	..	..	Contraction marked for age; accelerated flow
78	39	♂	250	175	1	2	3	..	..	+++	..	..	+++	..	+	Contraction marked for age with early disturbance in flow

* The grade of retinal sclerosis appeared more marked than the actual grade present because of perivascular gliosis.

three cases, being within normal limits in two and moderately reduced in one. It is important to point out that in sixty cases the blood urea was 40 mg. or less; in only sixteen cases was the blood creatinine abnormally high, ranging from 2.1 to 7.1 mg., and uric acid, when estimated, was never found above 5.1 mg. for each hundred cubic centimeters of blood.

The basal metabolic rate was determined in thirty-nine of the cases in the present series. In fourteen the rate was normal, varying between — 10 and + 10, and the thyroid gland on palpation was normal. In seventeen cases the rate varied between + 10 and + 20; in three of these, small adenomas of the thyroid were present, but clinical symptoms of hyperthyroidism were not present. In eight cases the rate was between + 20 and + 40, and this increased rate was maintained in the five in which a second estimation was made. In this group of eight cases, adenomas of the thyroid were present in two, but clinical evidence of

TABLE 5.—*Renal Function at Time Retinitis Was First Observed*

	Cases, Grouping Approximate	Phenolsulphonphthalein, per Cent	Specific Gravity, Range	Water Output, Cc.	Blood Urea, Mg.	Blood Creatinine, Mg.
Normal	21	45 to 75	1.003 to 1.025	1,100 or more	Below 40	Below 2.0
Mild insufficiency	46 (1)*	35 to 40	1.003 to 1.020	900 to 1,000	35 to 40	Below 2.0
Moderate insufficiency	7 (1)*	20 to 35	1.003 to 1.020	600 to 800	40 to 70	1.7 to 3.2
Severe insufficiency	7 (3)*	Below 20	Less than 1.003 to 1.020	Less than 500	80 to 144	2.1 to 7.1

* Cases in which myocardial decompensation was present.

hyperthyroidism could not be demonstrated. This moderately increased metabolism in eight cases was apparently not caused by a diseased thyroid. This increase in metabolism confirms the observations of Du Bois, Boas and Shapiro, and others.[10]

THE DEVELOPMENT AND COURSE OF THE SYNDROME

Two of the eighty-one patients had been examined five and ten years previous to the onset of retinitis for minor complaints, and hypertension or other abnormal cardiovascular lesions were not found. Four patients on previous examinations made within periods of three, five and seven years of admission revealed definite benign hypertension, but no retinitis. The longest record of hypertension was thirteen years, with retinitis typical of malignant hypertension demonstrable for the last four years

10. Peabody, F. W.; Meyer, A. L., and DuBois, E. F.: The Basal Metabolism of Patients with Cardiac and Renal Disease, Arch. Int. Med. **17**:980 (June) 1916. Boas, E. P., and Shapiro, S.: Diastolic Hypertension with Increased Basal Metabolic Rate, J. A. M. A. **84**:1558 (May 23) 1925. Boothby, W. M., and Sandiford, Irene: Laboratory Manual of the Technic of Basal Metabolic Rate Determinations, Philadelphia, W. B. Saunders Company, 1920.

of the patient's life. Such observations suggest that serious uncontrolled hypertension may develop primarily in persons whose cardiovascular systems had previously been normal and secondarily in others who have previously suffered from hypertension and general diffuse arteriosclerosis.

We have endeavored to keep in contact, by periodic examinations or by letter, with these eighty-one patients from the time that malignant hypertension was diagnosed. Fifteen of the patients returned for further examinations. Three of these died in Rochester. It was from the data collected in these fifteen cases that we are able to trace the course of the disease. As we noted previously, the cases group themselves into the cerebral, cardiac, renal and combined types.

Cerebral Type.—A typical example of this group (case 69, tables 1 and 2) was followed for a period of forty-four months from the time the diagnosis of malignant hypertension was made. During the first two years of our observation, the woman had attacks of numbness in the left arm and leg, with mild disturbance of speech. Later, weakness and numbness of the right leg were manifested. Two weeks before death, she had another apoplectic stroke, as the result of which death occurred in coma. Four months before death, renal function was practically normal.

Cardiac Type.—In four cases, marked cardiac insufficiency developed. In three cases it was manifested by severe respiratory distress, chronic passive congestion of the abdominal viscera and dependent edema. In one case the disturbance of cardiac function was shown by attacks of pulmonary edema and nocturnal attacks of Cheyne-Stokes respiration. In all of these cases there was slight renal insufficiency which was probably caused by chronic passive congestion and renal arteriosclerosis. Before the termination of the disease stupor and coma intervened, but the cerebral manifestations were not typical of those seen in the so-called uremic states.

Renal Type.—In three cases severe renal insufficiency developed between the time of the first and second examinations. Two of these patients died while under observation in the hospital; the third died one month after leaving the hospital. The maximal blood urea was 152 mg.; the maximal blood creatinine, 9 mg., and the minimal phenolsulphonphthalein excretion, 10 per cent. With these three cases should be considered two in which severe renal insufficiency was present at the time of the first admission. Death occurred in the hospital, the blood urea being 101 and 144 mg. and the creatinine 4.5 and 7.1 mg.; the clinical picture was similar (table 6). The important feature in these five cases is the mild anemia, or absence of anemia, even though the renal insufficiency was of a severe grade. This is explained by the short duration of the renal

TABLE 6.—*Studies of Renal Function in Fifteen Cases in Which There Were Two or More Admissions to the Hospital*

		Blood						Urine								
								Specific Gravity							Chloride Test, Percentage Concentration	
Case	Date	Hemoglobin, (Dare) per Cent	Hemoglobin, Gm. per Cent	Erythrocytes, Millions	Urea, Mg. per Cent	Creatinine, Mg. per Cent	Uric Acid, Mg. per Cent	Variation	With Concentration	With Water	Albumin Grade	Casts, Grade	Phenolsulphonphthalein, per Cent	Water Output, Cc.	Before Injection	After Injection
3	3/17*	..	....	....	..	...	...	1.024	.....	.....	1	...	50	.....	...	...
	11/22	76	....	4.58	32	...	3.2	1.002-1.031	1.028	1.001	0-1	0-1	55	1,005	...	...
	11/23	..	16.5	....	22	1.7	2.4	1.002-1.027	1.027	1.002	0-1	...	40	1,025	0.7	2.3
	4/25	75	16.9	4.21	31	1.3	2.5	1.005-1.028	1.028	1.005	0-1	...	40	.....	...	...
5	9/21	76	....	4.60	29	1.6	3.1†	1.001-1.027	1.027	1.001	1-3	1-3	60	1,145	...	...
	2/22	..	....	....	38	...	3.9	1.004-1.028	1.028	1.004	...	...	45	1,540	...	...
69	4/23	76	14.8	4.10	24	1.6	3.2	1.010-1.029	1.024	.....	0-Tr.	...	55	.....	...	...
	2/25	80	13.8	4.25	31	1.4	2.8	1.017-1.025	1.025	.....	Tr.	...	55	.....	...	...
	10/25	76	16.8	4.41	41	1.6	...	1.000-1.030	.....	1.000	1	Occasional	40	1,180	...	...
	5/26	70	....	4.64	31	1.1	...	1.012-1.017	.....	.....	Tr.	...	80	.....	...	...
	7/26	..	....	....	29	1.5	...	1.013-1.026	.....	.....	...	Occasional	80	.....	...	...
64	9/25	77	12.3	4.18	16-19	1.1	...	1.010-1.022	.....	.....	1	...	80	.....	...	...
	3/26	68	....	3.88	22	...	...	.....	.....	.....	1	...	..	.....	...	...
61	3/24	72	13.6	4.46	26-34	1.4-1.6	3.5-4.5	1.002-1.024	1.024	1.002	1	1	45	1,375	...	...
	2/25	80	....	4.90	21-44	1.4	...	1.002-1.021	.....	1.002	1	...	50	1,300	...	...
68	7/25	80	15.0	4.20	18	1.9	3.3	1.000-1.025	1.020	1.000	0-Tr.	Rare	60	1,325	...	...
	7/26	68	14.3	3.90	29-40	1.9	...	1.007-1.020	.....	.....	1-2	...	45	.....	...	...
36	11/25	70	13.8	3.83	30-34	1.7	...	1.010-1.020	.....	.....	1	2	40	.....	...	...
	4/26	75	....	4.36	33	1.6	...	1.011-1.016	.....	.....	...	...	35	.....	...	...
35	7/25	84	19.3	5.22	15	1.3	4.2	1.010-1.021	1.021	.....	0-2	1	50	.....	...	...
	12/25	85	....	5.68	36-45	2.1-2.3	...	1.001-1.022	.....	.....	2-3	2	20	.....	...	...
19	7/23	73	....	4.54	22	...	...	.....	.....	.....	...	1	35	.....	...	...
	11/23	..	....	....	40	2.2	4.8	1.005-1.020	1.020	.....	1	1	30	.....	...	...
46	5/25	82	....	4.72	30-36	...	...	1.005-1.026	1.026	1.005	1-2	Occasional	..	.....	...	...
	8/25	68	11.2	3.79	46	2.0	...	1.002-1.028	1.028	1.002	1	Occasional	35-40	840	...	...
53	3/22	75	....	....	26	...	...	1.003-1.030	1.030	1.003	1	Rare	45-55	710	...	...
	5/26	71	....	3.88	33-35	1.8-2.2	...	1.003-1.017	1.017	1.003	1	...	20	1,450	...	...
55	4/25	70	14.8	4.01	24-35	1.6	3.8	1.010-1.030	.....	.....	1-2	Rare	40	.....	...	...
	7/25	..	....	....	..	...	...	1.006-1.012	.....	.....	1-3	...	..	.....	...	...
65	6/25	71	17.9	4.02	28-34	1.4	3.4	1.003-1.025	1.025	1.003	1	Occasional	45	1,055	...	...
	7/26	68	....	4.30	34-43	1.7-2.5	...	1.002-1.030	1.030	1.002	Tr.	...	50	685	...	...
	9/25	71	15.9	4.04	85-108	3.1-6.8	...	1.003-1.011	.....	.....	1-2	Rare	25	.....	...	...
66	12/23	76	....	4.71	33	1.8	...	1.009-1.018	.....	.....	1-2	Rare	40	.....	...	...
	9/24	70	13.2	4.00	91-134	3.9-7.4	3.6-4.6	1.015-1.016	.....	.....	2-3	1	..	.....	...	...
47	3/25	73	....	4.29	33-40	2.0	...	1.001-1.023	.....	1.001	1-2	Rare	30	975	...	...
	2/26	66	....	3.93	67-152	5.7-4.6-9.0	...	1.001-1.017	.....	.....	1-2	Rare	10	.....	...	...

* Examination five years previous to diagnosis of malignant hypertension.
† Blood uric acid; Folin and Wu method: J. Biol. Chem. **38**: 81, 1919.

TABLE 7.—*Pathologic Data*

Case	Gross: Heart: Weight, Gm.	Gross: Heart: Myocardial Change, Grade	Gross: Coronary Sclerosis, Grade	Gross: Kidneys, Combined Weight, Gm.	Gross: Brain	Gross: Sclerosis of Large Vessels, Grade	Microscopic Changes: Cardiac, Grade	Microscopic Changes: Renal, Grade	Microscopic Changes: Cerebral, Grade	Microscopic Changes: Ophthalmic, Grade	Microscopic Changes: Smaller Vessels, Grade
26	715	.....	2	194	.....	..	Sclerosis of arterioles, 3	Chronic diffuse nephritis; arteriosclerosis, 2; sclerosis of arterioles, 4	.....	.....	Generalized sclerosis of arterioles, 4
32	870	Fibrosis, 3	1	366	.....	..	Sclerosis of arterioles, 3; myocardial fibrosis, 3	Chronic diffuse nephritis; arteriosclerosis, 3; sclerosis of arterioles, 4	.....	.....	Generalized sclerosis of arterioles, 4
37	400	.....	2	270	Areas of softening and of hemorrhage	1+	Sclerosis of arterioles, 3; fibrosis of myocardium, 1	Chronic diffuse nephritis; arteriosclerosis, 2; sclerosis of arterioles, 4	Arteriosclerosis, 3; sclerosis of arterioles, 4; areas of softening and hemorrhage	.....	Generalized sclerosis of arterioles, 4
45	...	.....	...	...	.....	..	.....	Chronic diffuse nephritis; arteriosclerosis, 3; sclerosis of arterioles, 3			
66	898	Fibrosis, 2	3	382	Areas of softening and of hemorrhage	3	Hypertrophy of myocardial fibrils and sclerosis of arterioles, 3	Arteriosclerosis, 3; sclerosis of arterioles, 4; chronic diffuse nephritis	Arteriosclerosis, 1; sclerosis of arterioles, 2; areas of softening and multiple areas of hemorrhage	Sclerosis of arterioles of choroid, 4; sclerosis of arterioles of retina, 2; areas of hemorrhage and exudates	Generalized sclerosis of arterioles, 4
80	496	Fibrosis, 1	3	206	Areas of softening and of hemorrhage	2-3	Slight hypertrophy of fibrils and sclerosis of arterioles, 2	Arteriosclerosis, 3; sclerosis of arterioles 4; chronic diffuse nephritis	Arteriosclerosis, 1; sclerosis of arterioles of vessels of subarachnoid space and brain, 2; areas of softening and hemorrhages	Sclerosis of arterioles of choroid, 4, and of retina, 2; areas of hemorrhage and exudates	Generalized sclerosis of arterioles, 4
81	870	Fibrosis, 2+	1	325	Areas of softening and old small areas of hemorrhage	2	Hypertrophy of myocardial fibrils and diffuse fibrosis, 2+; sclerosis of arterioles, 2	Arteriosclerosis, 3; sclerosis of arterioles, 4; chronic diffuse nephritis	In subarachnoid vessels: arteriosclerosis, 2; sclerosis of arterioles, 2. In brain: arteriosclerosis, 2; sclerosis of arterioles, 4	Sclerosis of arterioles of choroid, 4, and of retina, 1; areas of hemorrhage and exudates	Generalized sclerosis of arterioles, 4, also in skeletal muscles

insufficiency, which is in marked contrast to the extent of renal insufficiency and secondary anemia seen in the last stage of chronic glomerulonephritis.

From the course and terminal picture of this syndrome, we have abundant evidence that death is not due to the failure of any vital organ but to a severe widespread disease.

Combined Type.—Case 65 (table 1) is a typical example of this group. A man, aged 46, was first examined in June, 1925. For three years, the blood pressure had been elevated; he had been nervous and slightly dizzy at times and had suffered from frequent occipital headache. For five weeks before examination, vision in the right eye had been poor.

On examination, the patient seemed nervous and slightly apprehensive. He was large and apparently healthy, weighing 182 pounds (82.7 Kg.). The peripheral arteries were apparently sclerosed (graded 1). The heart was moderately enlarged, measuring 3.5 cm. to the right and 13.5 cm. to the left. Definite tachycardia was present, but no murmurs or other abnormal heart sounds were heard. Dyspnea, edema and anemia were not present. The systolic blood pressure was 240 and the diastolic, 145. The Wassermann test with the blood was negative. The electrocardiogram showed inversion of the T wave in lead 1. The basal metabolic rate was + 7 and + 15 on two occasions. The thyroid gland was not definitely abnormal. Ophthalmoscopic examination showed edema of the disk and retina, which was more severe in the right eye, apparent sclerosis (graded 3) of the retinal arteries, scattered hemorrhagic areas and cotton-wool and punctate exudates. The urine contained albumin (graded 1) and an occasional hyaline cast. The phenolsulphonphthalein output was 45 per cent in two hours and the water output 1,055 cc. in four hours. The specific gravity of the urine varied from 1.003 to 1.025. In the blood, the urea was 28 mg., creatinine, 1.4 mg., and uric acid, 3.4 mg. for each hundred cubic centimeters. Here, then, was a case characterized by high blood pressure, absence of anemia, good cardiac function (except for the inverted T wave in lead 1) and practically normal renal function, in which the retinal changes indicated a serious prognosis. While the patient was in the hospital, the blood pressure was reduced after a therapeutic bath to 200 systolic and 110 diastolic and, after ingestion of sodium nitrite, to 160 and 110, respectively. After two weeks of treatment, however, the systolic blood pressure was still 230 and the diastolic, 130.

Thirteen months later, the patient was admitted for the second time. He had been able to carry on his work during the intervening period, but was in much the same condition as on his first admission, both as to symptoms and physical condition. The systolic blood pressure was 240 and the diastolic, 150. The condition of the retina was unchanged, but

the electrocardiogram was negative. The blood count was not changed. The basal metabolic rate was + 14 and + 20 on two occasions. The blood pressure fell after a hot bath to 220 systolic and 120 diastolic, and after the ingestion of sodium nitrite to 175 and 120, respectively; it was not affected by phenobarbital. There was a trace of albumin but no casts in the urine; the specific gravity ranged from 1.002 to 1.030; the water output was delayed (685 cc.); the blood urea was from 34 to 43 mg., and the blood creatinine, from 1.7 to 2.5 mg. for each hundred cubic centimeters. Summarizing, the blood pressure was high and unchanged; the retinal picture was the same; no abnormality was disclosed by the electrocardiogram; slight renal insufficiency was indicated by the level of the blood urea and by diminished output of water. Although practically there had not been any change in the patient's general condition during the year, the retinal changes still made us feel that the prognosis was grave.

Five weeks later, in September, 1926, the patient was admitted to the hospital for the third time. For three weeks, he had been suffering from nausea and vomiting. At the time of examination he was nervous. The systolic blood pressure was 220 and the diastolic, 140. Anemia was not present. The edema of the disks and retina was slightly increased, and a number of fresh cotton-wool exudates and hemorrhagic areas were present. There was definite evidence of serious renal insufficiency, the blood urea being 85 mg., the creatinine, 3.1 mg., and the phenolsulphonphthalein excretion, 25 per cent. While the patient was in the hospital, the renal insufficiency became more marked and at times attacks of pulmonary edema occurred. One month later, in October, 1926, the patient died, cardiac and renal failure being the immediate cause of death. He had been delirious and comatose for forty-eight hours before death. The blood urea had risen to 108 mg. and the creatinine, to 6.8 mg. Permission for necropsy was not obtained.

This patient had known of the presence of hypertension for approximately four years. It is certain that the malignant type of hypertension had been present for sixteen months; yet it is significant that for thirteen of the sixteen months he enjoyed comparatively good health. Then rapid renal, cardiac and cerebral failure occurred, indicating the termination of a diffuse pathologic process.

Of the eight patients in this series who died in Rochester, the terminal illness was of the combined type in five, cerebral in two, and cardiac in one.

HYPERTENSION

The degree of hypertension was studied in each patient in the hospital. We observed the reaction of the heightened blood pressure to rest in bed, hot baths and the periodic use of sodium nitrite, phenobarbital and typhoid vaccine. After these measures, there was usually a tem-

porary fall of blood pressure. The actual minimal blood pressure obtained in this series was 140 systolic and 60 diastolic, following the ingestion of sodium nitrite. After phenobarbital was given, the minimal figures were 150 and 95; after a hot bath, 140 and 85, and after typhoid vaccine, 170 and 100. The rule in these cases was that the blood pressure continued at a high level despite the temporary falls. On admission, the diastolic blood pressure in seventy-two cases was above 120 mm. On dismissal, the diastolic pressure in forty-six cases still continued to be above 120 mm. That it is nearly impossible to lower the blood pressure permanently in these cases by our present therapeutic methods is clearly shown by the fact that, in forty-two of the present series, diastolic pressure was never reduced by any measures below 110 mm.

THE RETINA [11]

The retinitis is graded 1 to 4 on the basis of the amount of papilledema, the degree and extent of the retinal edema, the number of cotton-wool exudates and hemorrhagic areas and, in the later stages, the number and extent of exudates associated with absorbing edema, and the completeness and density of the macular star.

The grade of the retinitis refers to the severity of the retinal lesions. A retinitis of any grade has a definite course of development from onset to resolution, which is independent of its severity. This course is divided into four stages by definite differences in the appearance of the retinal lesions, the dividing lines of which, it is true, are not absolutely differentiated. Detailed data in each case are included in table 1.

A more detailed description of the ophthalmoscopic and histologic features of the retinitis of malignant hypertension with a discussion of its clinical significance was presented as a thesis to the American Ophthalmological Society and will be found in the transactions of the society for 1927.

The type of the retinitis and not its severity is characteristic of this group of cases. Edema of the disks is a striking feature in all the cases and is often disproportionate to the other retinal changes. All grades of the retinitis, from the mildest to the most severe, run a characteristic course which may be divided into four stages. In the first stage, hyperemia and mild edema of the disk and peripapillary retina, with a few superficial hemorrhagic areas and cotton-wool exudates, are present. In the second stage, the edema of the disk and retina becomes more marked and spreads into the macular region and periphery; the hyperemia continues; the hemorrhagic areas and cotton-wool exudates become more numerous and are found farther away from the disk and

11. The sclerosis of the retinal arterioles is graded 1 to 4 on the basis of the degree of constriction in caliber, of increased brightness of the reflex stripe, of the severity of the compression at the arteriovenous crossings, and particularly of the frequency and the extent of localized irregularities in the lumen of the arterioles.

in the deeper layers of the retina as well; a few punctate exudates are seen. In the third stage, the edema begins to recede from the peripheral part of the retina, and small spots of proliferated pigment are seen in its stead. Punctate exudates begin to outnumber the cotton-wool exudates, and arrange themselves into imperfect star figures in the macular region. The hemorrhagic areas are relatively fewer and are, in the main, more peripherally situated. The hyperemia of the disks is less evident and may gradually fade. As the retinitis progresses through these stages the associated sclerosis of the retinal arterioles becomes more marked, due partially to perivascular thickening and gliosis caused by edema of the surrounding retina. In the fourth stage, the disk has become definitely pale, and only blurring and increased glial tissue remain as evidence of the previous edema (secondary atrophy). Definite perivascular thickening along the walls of many of the vessels, the veins as well as the arteries, is seen. Atrophy has replaced edema of the retina, and only a few residual small punctate exudates may remain, usually in the macular region. Spots of proliferated pigment are numerous, especially in the macula and periphery. Patchy sclerosis of the choroidal arteries is noticeable. An occasional small hemorrhagic area may be present (figs. 2 and 3).

It is difficult to estimate the duration of the various stages of the retinitis, as we have not been able to follow any one case continuously through all stages. On the basis of subjective visual complaints, the retinitis had existed for an average of four months in the cases observed in the second stage. In those in which the retinitis was in the third stage, it had existed for an average of six and a half months. The retinitis in one patient had progressed from the first to the second stage by the end of four months. In another, it had progressed from the second to the third stage by the end of two and a half months, and in one from the first to the third stage by the end of one year. In two cases in which at first observation, the retinitis was in the second stage, it had advanced to the third stage a year later. In one case, the retinitis had progressed from the third to the fourth stage after eleven months. Apparently the first stage is the shortest or has the least effect on vision, patients having been seen in whom the retinitis was definitely in the second stage one week after the onset of visual disturbances. The third stage is the longest and the most frequently observed. In one case, the retinitis was still in the third stage at least forty months afer the onset. In the case manifesting the most definite fourth-stage retinitis, the disease had started about three years previously.

In sixteen cases, it was possible to observe the course of the retinitis at intervals for a considerable period. In six cases, the retinitis progressed in stages but maintained about the same grade of severity during the period of observation. In six other cases, the retinitis

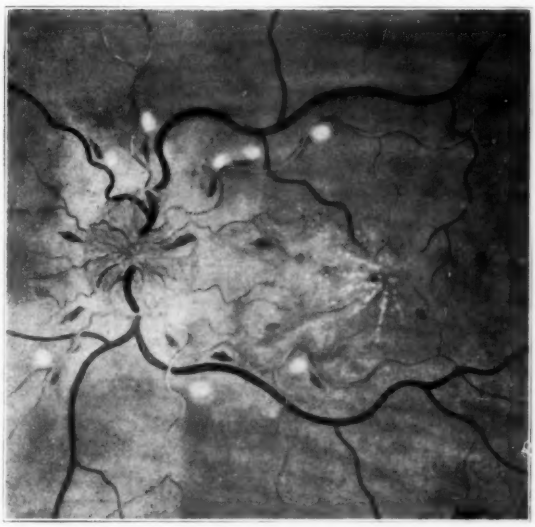

Fig. 2.—Retinitis (stage 2 to 3) of malignant hypertension (diagram).

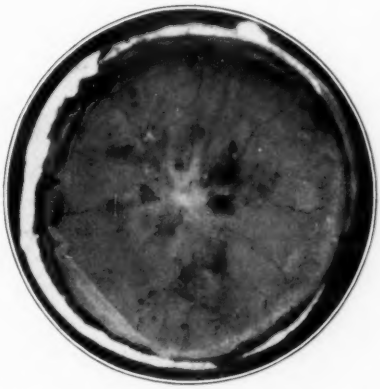

Fig. 3 (case 81).—Posterior half of eye, showing edema of optic disk, hemorrhages and exudates; × 2.5.

progressed in both stage and grade. The sclerosis of the arterioles especially showed a definite tendency to increase in grade. The retinitis regressed in only four cases. One mild case of retinitis subsided completely before the patient's death, and left only vascular residuals. Typical fourth-stage retinitis with secondary optic atrophy was seen in only one case; cerebral decompression had been performed elsewhere for suspected tumor of the brain. Whether this operation was a factor in accelerating the resolution of the retinitis is difficult to say. It is interesting in this connection, however, to recall that Cushing and Bordley [12] think that increased intracranial pressure, with resultant increased fluid pressure in the intervaginal spaces of the sheath of the optic nerve, is a factor in causing the edema of the disk and retina in the retinitis of nephritis. Three cases of typical retinitis and moderate to severe sclerosis of the retinal arterioles had been observed from two to six years previously, at which time the mild arterial change was the only abnormality in the retina. In two cases in which mild retinitis of the type of benign hypertension had once been observed, retinitis of malignant hypertension was found later.

PROGNOSIS

The seriousness of this disease is shown by the fact that of the eighty-one patients, seventy-four (91 per cent) died within fifty-one months, the majority within two years. Only five patients lived two years or longer. The average length of life after diagnosis was eight months. Our data concerning the terminal illness is somewhat meager: sixty-six patients died at home, and the physicians recorded only the chief cause of death. A few, however, described the course of events, which was similar to that in the eight cases we had observed.

PATHOLOGIC DATA

A postmortem examination was made in seven cases. Four of these examinations were fairly complete, two only partially so, and one was carried out elsewhere, only sections of the kidney being sent for microscopic examination. The detailed changes noted grossly and microscopically are given in the tables. The following description is a summary of the pathologic data in cases 26, 32, 37, 45, 66, 80 and 81 (table 7).

The gross changes are really not characteristic, and only a few were constant throughout. Edema may be absent but when present varies much as to site and extent. The heart is always hypertrophied, but the degree is not constant; in the cases in which there is a long history of hypertension there is usually a high degree of cardiac hypertrophy, while,

12. Cushing, Harvey, and Bordley, James: Subtemporal Decompression in a Case of Chronic Nephritis with Uremia; with Especial Consideration of the Neuroretinal Lesion, Am. J. M. Sc. **136**:484, 1908.

when the history is short, the hypertrophy is of lesser degree. Coronary sclerosis is usually graded 2 and apparently is not dependent on the cardiac hypertrophy or on the age of the patient. Sclerosis of the aorta also varies in degree in different cases, the average being slightly less than grade 2. There is nothing constant about the changes in the kidneys, although they usually show evidences of arteriosclerosis; sometimes they

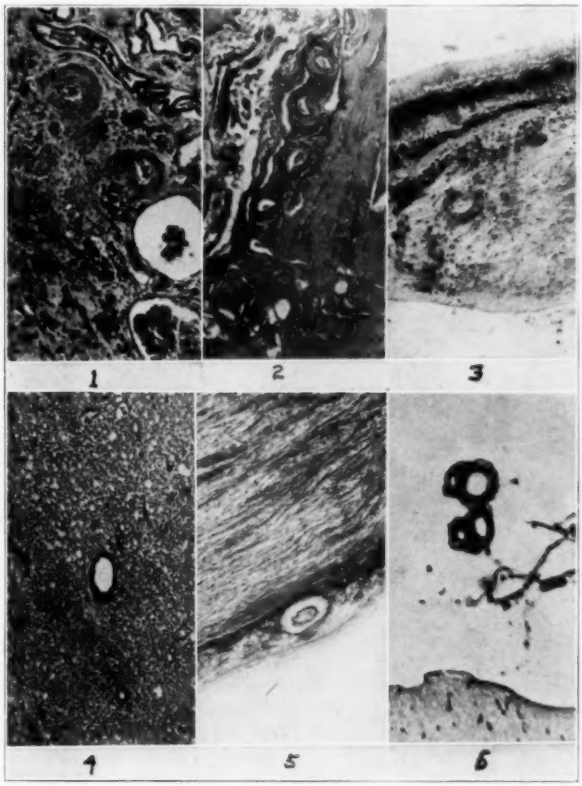

Fig. 4 (case 81).—Arteries from various organs: 1, kidney; 2, skeletal muscle; 3, retina; 4, brain; 5, choroid; 6, subarachnoid vessels.

are atrophic and shrunken, but more often the combined weight is only slightly less than normal. In the four cases in which the brain was examined, definite evidence of arteriosclerosis was present. The vessels in the subarachnoid space and in the circle of Willis as a rule show mild sclerosis. In the coronal sections of the brain, multiple areas of softening were seen; whether these softened areas are due to minute hemor-

rhages or simply to occlusion of vessels is difficult to determine. Occasionally, a severe hemorrhage was encountered which had caused definite clinical symptoms and possibly was the immediate cause of death.

In the microscopic studies of the tissues there are several important features; the most outstanding are the diffuseness of the lesions and the degree of involvement of the smaller arteries and arterioles, while the larger arteries and the capillaries are comparatively free from change (fig. 4). The changes in the arterioles are different from those observed in the arteries of old persons: there is more marked hyperplasia of the intima and hypertrophy of the media and internal elastic lamina (fig. 5) in contrast to the degenerative changes in senile arteriosclerosis with

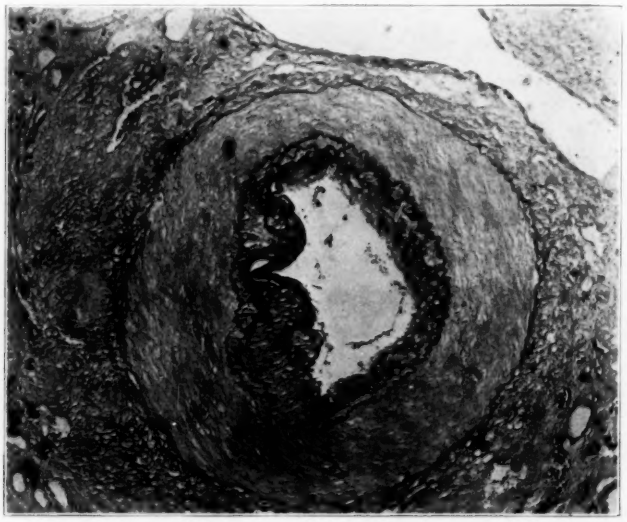

Fig. 5.—Small artery of kidney showing thickened media, hypertrophy and splitting up of internal elastic lamina. Narrowing of lumen and perivascular fibrosis. Weigert's elastic tissue stain; × 60.

their deposits of lipoids, fatty acid and calcium in the intima and fragmentation but little hypertrophy of the internal elastic lamina. Again, in senile arteriosclerosis the smaller arteries and arterioles do not manifest the extensive intimal hyperplasia and the marked narrowing of the lumina which is so definite in these cases of malignant hypertension. Perivascular fibrosis of varying degrees of intensity is present. Sometimes fibrosis is diffuse throughout the organ, while in the brain the diminution of the blood supply causes softening and formation of cysts (fig. 6) rather than gliosis. These areas of softening in the brain are not limited to any one region but are usually scattered more or less diffusely through-

out the organ, although they may be more severe in one area than in others. These collected areas of softening vary in situation in different cases, but they are not particularly evident in the floor of the fourth ventricle or around the aqueductus cerebri, nor is the sclerosis of the arterioles more marked in these areas. An interesting but unexplained observation is that the degree of vascular obstruction is much milder in the retinal vessels (figs. 7 and 8) than in the choroidal vessels (figs. 7 and 9) and also that it is less in the vessels of the subarachnoid space than in the vessels supplying the brain substance proper. Thus the retinal and subarachnoid vessels are comparable in degree of sclerosis as are those of the choroid and the brain.

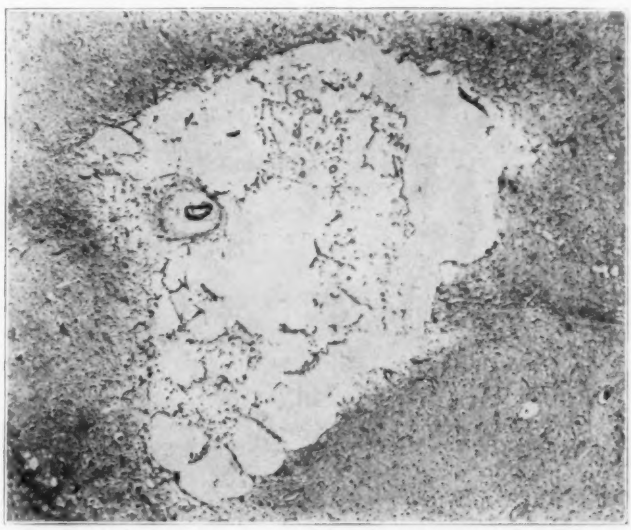

Fig. 6.—Area of softening in the brain. The small artery in the center is not occluded as a result of either sclerosis or thrombosis. Hematoxylin and eosin; × 30.

Throughout the retina but especially around the disk and the macula, considerable numbers of homogenous masses that stain with eosin are present. The larger and more recent ones seem to be in the superficial layers of the retina (fig. 10), while the smaller, the more numerous and apparently the older ones are in the internuclear layer. The smaller masses are in what appears to be different stages of absorption (fig. 7); large phagocytic cells that contain fat are near them, sometimes in the margin and sometimes within the mass, while in some areas little else but these fat cells can be seen (fig. 11). The collections of these cells that contain fat suggest that complete phagocytosis of previous

similar masses has taken place. The hemorrhages have a similar distribution to the so-called exudates; large areas of recent hemorrhages are seen in the layers of ganglion cells and nerve fibers (fig. 12), while numerous, small and older ones are present in the internuclear layer.

The most important and constant feature of these cases is the extreme diffuseness of the lesion; not a single organ or tissue escapes, and even the vessels of the gastro-intestinal tract and the skeletal muscles are equally severely involved (fig. 4). Sometimes the kidney, the heart or the brain is more severely injured, but not any organ escapes. The

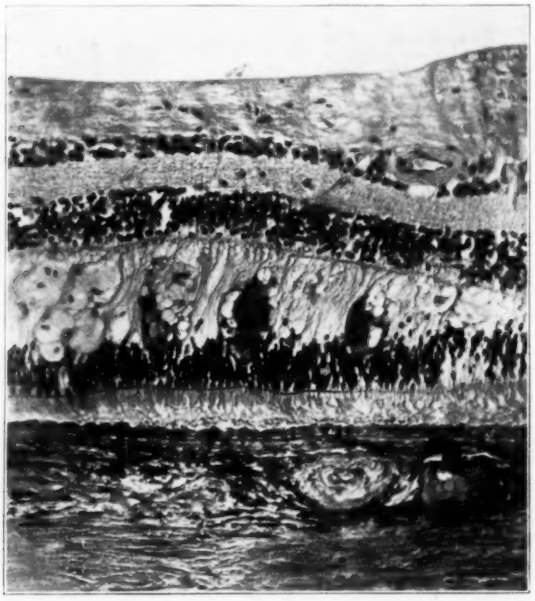

Fig. 7.—Exudate in the internuclear layer of the retina. Different stages in the process of absorption can be seen. The relative sclerosis in the retinal and choroidal arterioles should be noted. Hematoxylin and eosin; × 120.

kidneys in every case show profound changes, all of which can be attributed to the severe vascular injury chiefly of the smaller arteries and arterioles (fig. 13). The capillaries are almost unaffected, except in the glomerular tufts where the nuclei are apparently more numerous. The glomerular tufts themselves show marked changes, but they are different from those observed in glomerulonephritis. Some glomeruli are completely fibrosed, others only partly so, as the tuft may be lobulated and one or several lobules fibrosed and the others intact. Some glomeruli are apparently normal and are even hypertrophied, the only change being

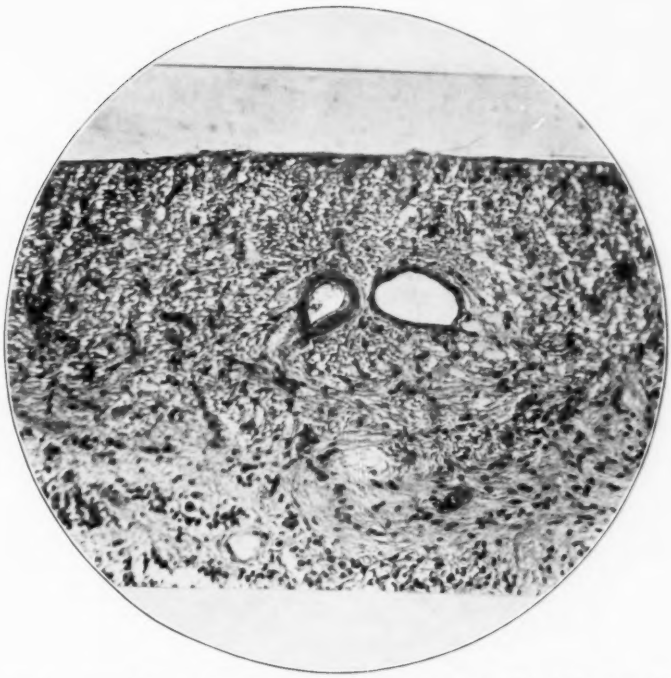

Fig. 8.—Arteriole and venule of the retina at the optic disk. There is slight thickening of the walls of the arterioles, but it is of a minor degree compared with choroidal arterioles. The edema and the increase in glial tissue also should be noted. Hematoxylin and eosin; × 200.

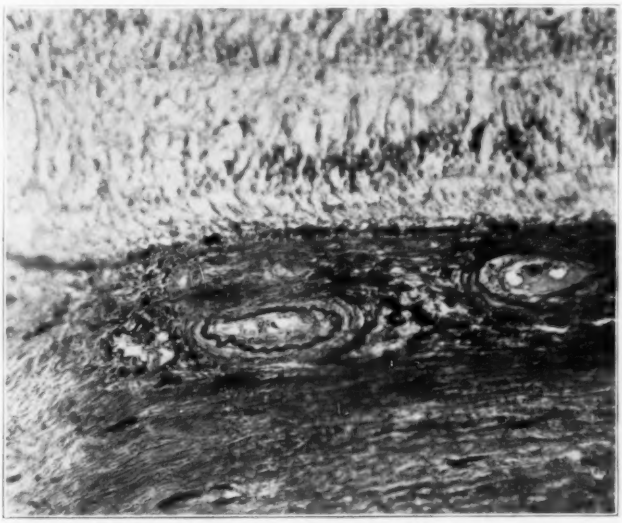

Fig. 9.—Arterioles of choroid showing thickening of walls, hypertrophy of internal elastic lamina with almost complete occlusion of lumina. Weigert's elastic tissue stain; × 120.

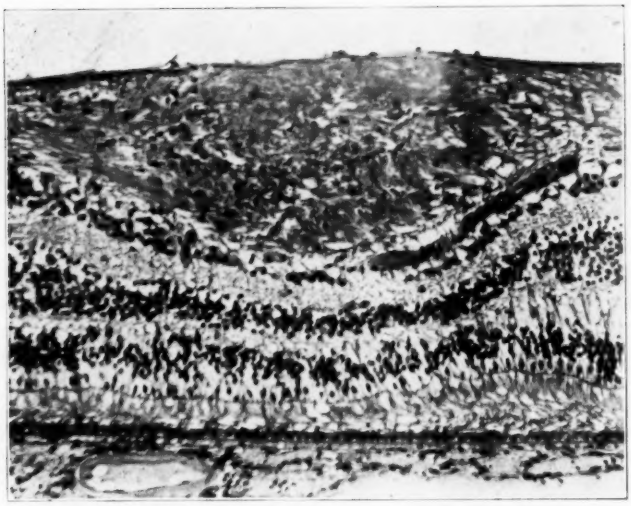

Fig. 10.—Large exudate and some cytoid bodies in the layer of nerve fibers of the retina. Hematoxylin and eosin; × 120.

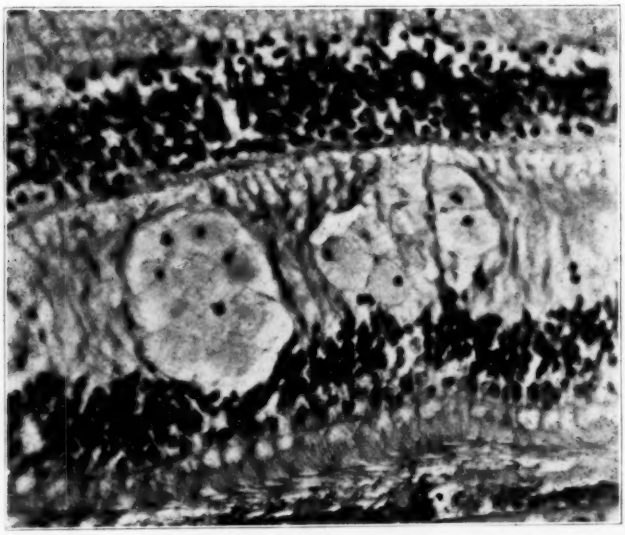

Fig. 11.—Complete replacement of exudates in the internuclear layer of the retina by large clear "scavenger" cells. Hematoxylin and eosin; × 225.

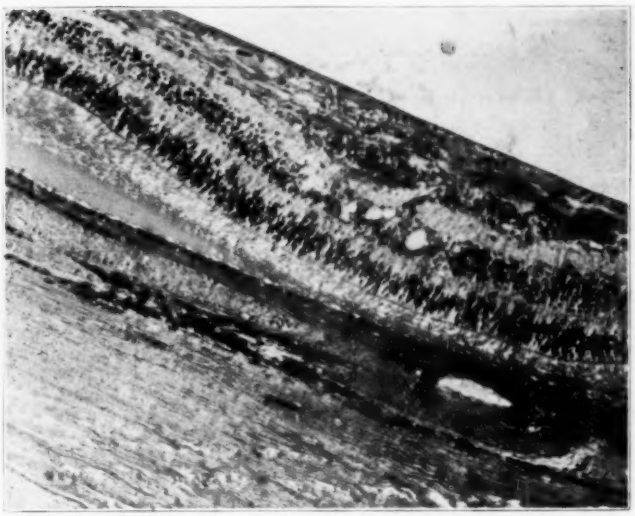

Fig. 12.—Recent hemorrhage in the layer of nerve fibers of the retina. Homogeneous exudate between retina and choroid. Hematoxylin and eosin; × 100.

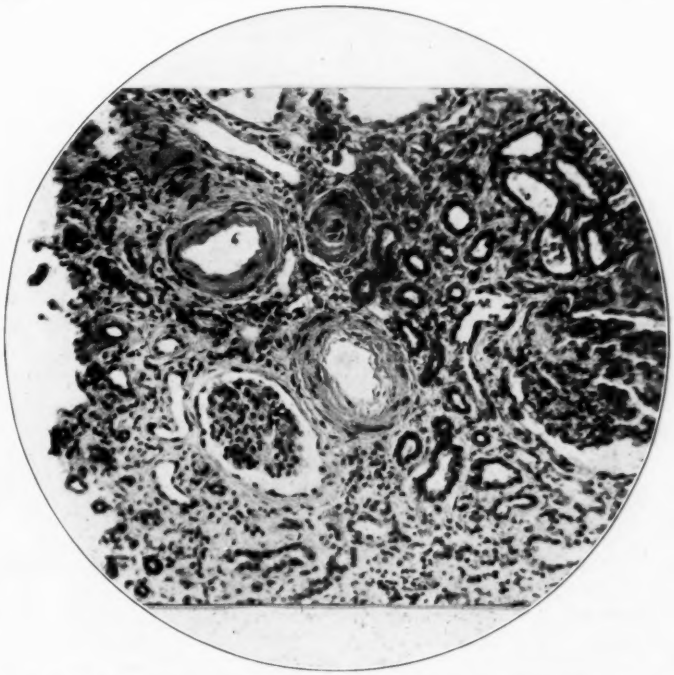

Fig. 13.—Small arteries and one arteriole of kidney. Almost complete occlusion of lumen of the arteriole by the intimal and medial proliferation. Arterial walls thickened. The comparatively good glomerulus with some increase in the endothelial cells of the tuft should be noted. Hematoxylin and eosin; × 200.

an apparent increase in the endothelium of the capillaries. Extensive interstitial fibrosis and destruction of some of the tubular epithelium, with little evidence anywhere of true inflammation, are present. All these changes can be attributed to the severe ischemia of the kidney and do not resemble any of the primary diffuse renal lesions.

COMMENT

Owing to the diffuse vascular changes in this disease, the abnormal symptoms will necessarily be varied, and these may or may not be typical of any characteristic syndrome associated with disease of a single organ. We have dwelt particularly on the symptoms arising from cerebral and retinal lesions, and yet frequently these are not especially noted by the patients themselves. The reserve of cardiac muscle may be greatly reduced and yet symptoms referable to a failing heart may be slight or absent. Typical symptoms due to renal disease are infrequent; similarly, evidence of angina pectoris, intermittent claudication, and other peripheral arterial lesions are uncommon; anemia is rare. The vagueness of the symptoms and the paucity of physical defects make one wonder whether simply persistent marked hypertension constitutes a serious disease; yet the course of these cases is truly malignant. Careful consideration reveals further objective signs, the most significant of which is the retinal lesion: the electrocardiogram often reveals disease of the myocardium; renal tests may show minor functional defects; palpation may indicate diffuse sclerotic changes in the arteries; the ophthalmoscope may suggest similar changes in the retinal arterioles, and examination of the capillaries of the nail-fold reveals abnormal blood flow and even contraction and tortuosity. The terminal picture is often obscure and strikingly suggests simultaneous rapid failure of the vital functions of the brain, heart and kidney. Our pathologic data confirm the observations that this syndrome is associated with extremely diffuse arterial disease.

Allbutt,[13] Janeway[14] and others have reported many cases of patients having benign hypertension or hyperpiesia. They followed the course for several years and have shown that these patients may live comfortably to old age. Renal, cardiac, cerebral and retinal functions remain adequate. Since the time of Bright,[15] diffuse vascular disease

13. Allbutt, T. C.: An Address on Arteriosclerosis and the Kidneys, Brit. M. J. **1**:853 and 922, 1911; Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915, p. 10.

14. Janeway, T. C.: Nephritic Hypertension: Clinical and Experimental Studies, Am. J. M. Sc. **145**:625, 1913.

15. Bright, Richard: Albuminous Urine of Four or Five Years Continuance; Death with Convulsions and Apoplexy; Kidneys Degenerated, Guy's Hosp. Rep. **1**:358, 1836.

has been recognized in association with chronic glomerulonephritis. Distinctive features of this disease, besides hypertension, are anemia, severe renal insufficiency, retinitis and a progressive downward course. Malignant hypertension can be distinguished from the benign form by the persistently high blood pressure and the rapid course. It may arise apparently ipso facto, particularly in the young, but frequently it is a later stage of the benign type. The course in both malignant hypertension and chronic glomerulonephritis may be stormy and rapidly fatal, but there are many dissimilar features. Anemia and renal insufficiency that are so characteristic in the one may be absent in the other. We believe that the retinitis can often be differentiated. In malignant hypertension the edema of the retina is less extensive and less dense, and there is little tendency to the formation of peripapillary snow-bank exudates. Edematous detachment of the retina was seen in only one case in the present series. The hyperemia of the disk is in marked contrast to the anemia of the disk and the retina that is seen in the retinitis of nephritis. Sclerosis of the retinal arterioles is always present in malignant hypertension and is usually absent in chronic nephritis. It is interesting that as long ago as 1884, Michel [16] recognized the serious prognostic import of retinitis in cases of chronic nephritis. Some of his patients in all probability had malignant hypertension, though the cases were not so differentiated by him. A definite relationship is not evident between the severity of the retinitis of malignant hypertension and the degree of impairment of renal function. Severe retinitis occurs with adequate renal function and without retention of urea. However, retention of urea is more often present when the retinitis is severe than when it is moderate. We believe that there are patients who have potentially malignant hypertension in whom retinal arteriosclerosis alone is evident or in whom arteriosclerosis with hemorrhages and exudates is present, but no edema of the disk. In the present series, however, only the cases in which definite papilledema was evident are included.

In the development of chronic glomerulonephritis, the kidney is severely injured and impairment of renal function occurs early. Hypertension develops gradually, and vascular fibrosis may be a late manifestation. This is particularly true in the retinal arterioles. On the other hand, at the onset of malignant hypertension, renal impairment may be difficult to demonstrate and develops only in the terminal stages, while changes in the arterioles appear early, especially in the retina. Thus, in malignant hypertension the renal involvement appears to be secondary to vascular lesions which are common to many viscera. Moreover, chronic glomerulonephritis usually occurs in the second or third decade, while malignant hypertension develops in the fourth decade. This fact

16. Michel, J.: Lehrbuch der Augenheilkunde, Wiesbaden, J. F. Bergmann, 1884.

was pointed out by Fahr and by Ellis and Marrack.[17] Further evidence is also present that vascular changes may occur in the apparently normal person and that other vascular diseases are prone to develop in the fifth decade; Brown[18] has pointed out that distinct changes in the capillaries of the nail-folds may occur in normal persons between the ages of 40 and 50, and that thrombo-angiitis obliterans occurs most frequently between the ages of 30 and 50.

One of the earliest microscopic studies of this condition was that of Gull and Sutton,[19] in 1872. They described an arteriocapillary fibrosis which they thought was allied to senile alteration. They also pointed out the diffuseness of the vascular lesion and demonstrated a similar thickening in the vessels of the subarachnoid space and in the kidneys. Their idea of the capillary involvement has not been universally substantiated, but the diffuseness of the lesion of the arterioles is even more extensive than they described. Demonstrable morphologic changes in actively functioning capillaries of the nail-folds have been shown to be infrequent. This is in harmony with the absence of general involvement of the capillaries in the tissues examined histologically. In 1914, Volhard and Fahr described the condition of "malignant sclerosis" or "bösartig hypertension"; this condition is analogous, but usually of a somewhat later stage, to that which we are describing under "malignant hypertension." They stress the thickening of the walls of the arterioles and the smaller arteries of the kidney, which leads to ischemia of that organ and subsequent parenchymatous changes. They found and emphasized the serious prognostic import of retinitis. They considered the pathologic changes in the retina to be due to primary ischemia of the arterioles as they are in the kidney.

One outstanding fact in this series of cases is the diffuse change in the arterioles. This is visible in the retina during life and in the tissues generally on histologic examination. The detailed microscopic changes in the wall of the arteriole include a thickening or hypertrophy of its three anatomic divisions. The noticeable thickening of the intima and the hypertrophy of the elastic fibers and media make a distinct picture. The almost total absence of signs of degeneration is in con-

17. Ellis, A. W., and Marrack, J. R.: An Investigation of Renal Function in Patients with Retinitis and High Blood Pressure, Lancet **1**:891, 1923.

18. Brown, G. E.: Capillary Observations in Cardiovascular Renal Disease, Ann. Clin. Med. **1**:69, 1922. Brown, G. E., and Allen, E. V.: Thrombo-Angiitis Obliterans, unpublished data. Brown, G. E., and Roth, Grace M.: Biomicroscopy of the Surface Capillaries in Normal and Pathologic Subjects, M. J. Australia **1**:499, 1927.

19. Gull, W. W., and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called "Chronic Bright's Disease with Contracted Kidney," Tr. Medico-Chir. Soc. London **55**:273, 1872.

trast to the many evidences of degeneration in the arteries in cases of senile arteriosclerosis. This lesion of the arteriole suggests hypertrophy which, if steadily progressive, would ultimately lead to occlusion of the lumen of the arteriole. Such occlusions are sometimes found. This is strong evidence in favor of the ischemia hypothesis of Volhard, which offers a logical explanation for the diffuse parenchymatous lesions found in this syndrome.

The association of sustained marked hypertension with diffuse change in the arterioles raises the question whether hypertension or the lesion of the arteriole is primary. So much evidence of hypertrophy in the wall of the arteriole suggests hypertrophy in the face of excessive strain. This interpretation would mean that the change in the arteriole is secondary to the hypertension. If, on the other hand, the diffuse lesion of the arteriole is primary, sustained hypertension might result on account of increased peripheral resistance. Our experience would lead us to consider the hypertension primary, but further study in the early stages of the disease will be necessary to decide the question.

There have been several contributions in which an endeavor has been made to find the primary cause of the hypertension. Bordley and Baker [20] attempted to explain it on the grounds of sclerosis of the arterioles of the medulla oblongata, their work being based on some experimental results of Anrep and Starling,[21] who demonstrated certain definite changes in the general blood pressure that were due to alterations in the blood pressure in the vessels to the medulla. Our histologic studies have not shown more marked changes in the arterioles in the medulla than elsewhere in the brain. Numerous contributions on benign or essential hypertension have been made, including the works of Huchard,[22] Allbutt, Janeway, Shaw [23] and Fishberg,[24] but in general, no serious attempt has been made to distinguish the malignant from the benign type.

The hypertrophied state of the arterioles suggests that the normal effect of vasoconstriction has been aggravated, generalized and made more or less permanent. Whether this phenomenon is due to stimulation of the endings of the sympathetic nerves by pressor substances in

20. Bordley, J., and Baker, B. M.: Consideration of Arteriosclerosis of the Cerebral Vessels and Pathogenesis of Hypertension; Preliminary Report, Bull. Johns Hopkins Hosp. **38**:320, 1926.

21. Anrep, G. V., and Starling, E. H.: Central and Reflex Regulation of the Circulation, Proc. Roy. Soc. Med. **97**: series B, 463, 1925. Starling, E. H.: The Physiological Factors of Hyperpiesia, Brit. M. J. **2**:1163, 1925.

22. Huchard, H.: L'artério-sclérose, Presse méd. **61**:769, 1909.

23. Shaw, H. B.: Hyperpiesia and Hyperpiesis (Hypertension), London, Frowde, Hodder and Stoughton, 1922, p. 191.

24. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925.

the circulating blood, to the direct effect of such substances on the musculature of the artery or to some more general disturbance of the sympathetic nervous system is a problem that not only is difficult of solution, but that also is of general importance in the etiology of hypertensive vascular disease.

SUMMARY

In cases of sustained high blood pressure and diffuse change in the arterioles, the course of the disease is usually rapidly fatal. The terminal clinical picture suggests simultaneous rapid functional failure of the brain, heart and kidneys. This hypertension syndrome can often be distinguished from benign hypertension and chronic glomerulonephritis. The chief points of distinction from the latter are the age incidence, the characteristic retinal picture, the absence of anemia, and the frequent adequacy of renal excretion. The characteristic histologic observaton is diffuse general hypertrophy of the arterioles.

EXPLANATION OF TABLES

Tables 1 and 2 contain the history and the physical and laboratory observations in each case, in tabulated form, and the gross and microscopic pathologic observations in seven cases are given in table 7.

PATHOLOGIC DATA

CASE 1 (case 66, table 7).—Edema (graded 2) was present in the lower extremities and to a lesser degree (graded 1) in the upper extremities; the peritoneal and pleural cavities were free from gross change but the pericardial cavity contained 50 cc. of clear straw-colored fluid. The heart weighed 838 Gm.;[25] the cavity of the left ventricle was small, and antemortem thrombus was present in the right auricular appendix. Several depressed whitish fibrotic areas were present in the wall of the left ventricle, each measuring 1 cm. in diameter. The walls of both ventricles were definitely hypertrophied, the left being 2.5 cm. and the right, 1.3 cm. thick. Well marked arteriosclerosis (graded 3) and thickening of the walls of the coronary arteries were present, but the lumina were patent throughout. Slight edema was present in the right lung but the left did not show a gross lesion. The spleen weighed 261 Gm. and the liver, 1,735 Gm.; chronic passive congestion was present in both. Definite edema (graded 2+) and congestion of the mucosa of the stomach and the small intestine were present.

The left kidney weighed 160 Gm. and the right, 142 Gm. The surface of the left kidney was uniformly granular, with many minute bleeding points. On section the cortical markings were indistinct, and the line of demarcation between the medulla and cortex was irregular and indistinct. On the surface of the right kidney were several prominent cortical scars, the largest of which was 1 cm. in diameter; the pelvis was dilated (graded 2+) and many subepithelial punctate areas of hemorrhage were present. Otherwise, the right kidney resembled the left.

25. The estimated normal weight of the heart for a female of this age, height and weight was 350 Gm.

Arteriosclerosis of the aorta (graded 3) was present, with extensive ulceration of the descending thoracic aorta and calcification of the abdominal portion. The ostia of the celiac and superior mesenteric arteries were partially occluded.

The brain showed atrophy (graded 2) of the convolutions with widening of the sulci and increase in the amount of the cerebrospinal fluid in the subarachnoid spaces. Arteriosclerosis (graded 3) of the vessels in the circle of Willis and of their branches was present. After fixation, the brain was cut by coronal sections at 1 cm. intervals. Fresh hemorrhage (a mass 2 cm. in diameter) was evident at the level of the postcentral gyrus near the corpus callosum in the corona radiata. There were also many small areas of softening in the midbrain in the region of the medial lemnisci and pons. These areas were rust-colored and diffuse. With a hand lens, the smaller vessels in this portion of the brain were seen to be prominent, having apparently thickened walls and narrowed lumina; multiple minute areas of softening were scattered diffusely throughout, especially in the nuclei of the cerebellum.

Microscopically, changes were noted in the kidneys, especially in their smaller arteries and arterioles. The arterial lumina were diminished, and the walls were hypertrophied or thickened. This thickening was of a peculiar nature: there was evidence of hyperplasia of the intima and accompanying this were hypertrophy and splitting up of the internal elastic lamina, as is usually seen in arteriosclerotic changes. However, hypertrophy of the muscular tissue of the media as well as an increase of the fibrous tissue in and around the adventitia was also evident. In the arterioles there was disproportion of the normal relationship between the thickness of the walls and the lumina of the vessels, the lumen in many vessels being almost completely, or wholly, obliterated. A varying degree of perivascular fibrosis occurred. Most of the capillaries appeared normal, with only occasionally slight hyperplasia of the endothelium or fibrosis around them. The capillary tufts of the glomeruli showed an increase in the number of nuclei, while the tufts in some places were adherent to each other, thus causing a lobulated appearance in many instances. Besides these evidences of vascular disease in the kidneys, other changes were present throughout the parenchyma. Some glomeruli showed changes, being completely hyalinized; others were only partly hyalinized, but many were normal. These changes were different from the crescent formation and the other changes characteristic of glomerulonephritis. The tubules were also affected to a lesser degree. In some places they were irregularly dilated, with flattening of the epithelium, and the lumen contained hyaline casts or cell debris; in other places, they were collapsed and obliterated. Throughout the entire kidney, there was marked interstitial fibrosis in the midst of which was abundant evidence of destroyed tubular epithelium. There were also some discrete masses of lymphocytes. A scharlach R stain revealed the presence of a small amount of fat in the epithelium of some tubules and in the intima of a few arterioles, but not in the glomeruli.

The arteries in the spleen showed marked thickening of the media and adventitia. The internal elastic lamina was hypertrophied and in many places split up, and a minor degree of hyperplasia of the intima was present. The external elastic lamina was also hypertrophied and split up. The arterioles showed slight adventitial fibrosis and the internal elastic lamina was hypertrophied and split; as in the arteries, the external elastic lamina was hypertrophied and divided into many fine layers of elastic tissue. Between these two elastic laminae, the media appeared to be composed of fibrinohyalinoid tissue rather than of true muscle tissue. Intimal proliferation could occasionally be observed, and some medial hyperplasia was seen. Little reticular fibrosis was present.

Throughout the parenchyma of the pancreas there was mild interstitial fibrosis, but the islands apparently were unaffected. The arteries and arterioles showed changes similar to those seen in the kidneys, but less marked. Certain small vessels, as in the kidney, showed a change with hypertrophy and splitting up of the internal elastic lamina and fibrosis of the adventitia. Occasionally slight thickening could be seen in certain capillaries, but the majority of these vessels were free from any appreciable change.

The arteries in the liver were considerably thickened and showed changes similar in degree to those in the pancreas; the arterioles were affected to a like extent; the media manifested muscular hypertrophy and an excessive amount of fibrous tissue was present in the adventitia. The elastic tissue was hypertrophied, and the intima was hyperplastic. The sinusoids were dilated but fibrosis was absent, with the exception of that already mentioned.

The vasa vasorum of the aorta had definitely thickened walls; the elastic tissue was slightly hypertrophied; the intima was increased in thickness, and excess fat was present in this coat. The coronary arteries showed slight arteriosclerotic changes similar to those seen in patients of this age, but the arterioles of the myocardium had thickened walls and narrowed lumina, although to a much less degree than those in the kidneys. Many of the individual fibrils of the myocardium were hypertrophied to several times their normal size but were free from fat; diffuse fibrosis was seen throughout the muscular tissue, which in places was completely replaced by dense bands of fibrous tissue. The capillary walls were not fibrosed or thickened.

The arteries and arterioles of the lung were slightly involved in this general change but less than in most other organs and, as elsewhere, the capillaries appeared to be almost free. A considerable number of the so-called heart failure cells were present in some of the alveoli. Few arterioles were seen in the suprarenals, but the ones that were present had thickened walls and narrowed lumina. Several were obstructed by the presence of antemortem thrombi, but showed early canalization.

The vessels in the brain were less affected than those of other organs. Those in the subarachnoid space were undoubtedly thickened but to a much less degree than those of the kidneys. The ratio of vessel wall to lumen in the arteries was almost normal. In the arterioles the walls were slightly thickened, but splitting of the internal elastic lamina was not observed. The intima was hyperplastic, the media did not show hypertrophy, and there was slight perivascular fibrosis and thickening of the adventitia. In the brain tissue proper, the same changes existed, except that occasionally an arteriole was encountered with definite general thickening of its walls. The smallest arterioles showed slight intimal hyperplasia. It was difficult to determine whether these small vessels were arterioles or capillaries. The capillaries showed a slight increase in the number of nuclei in their walls, but other appreciable change could not be distinguished. Vessels from different areas of the brain were examined (fourth ventricle, midbrain, basal nuclei and various places in the cortex), and these observations were consistent throughout. Areas of hemorrhage and numerous small areas of softening contained considerable amounts of blood pigment with numerous "scavenger" cells, and the vessels supplying some of these areas seemed to be partly occluded by proliferation.

In the eye the choroidal vessels were definitely thickened, and the lumina was narrowed sometimes even as much as in the renal vessels. Proliferation of the intima was present. The media was hypertrophied, and perivascular fibrosis was present. Occasionally an arteriole was encountered in which the lumen was completely occluded by the intimal proliferation (fig. 14). In the retinal

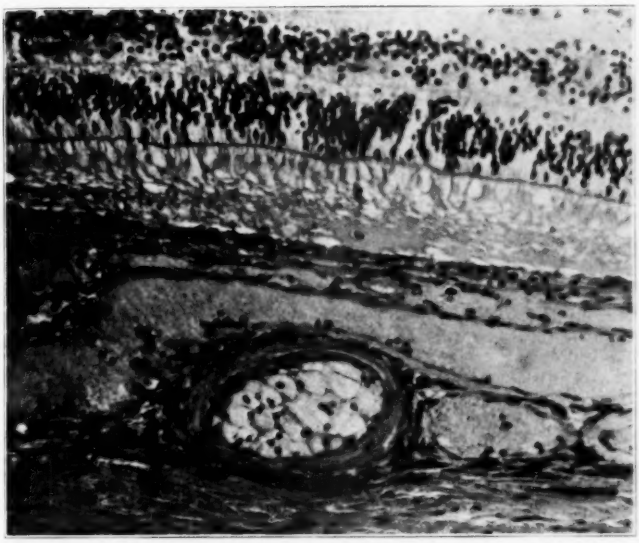

Fig. 14.—Complete occlusion of one of the choroidal arterioles and a proliferation of the retinal pigment epithelium between the choroid and the retina. Hematoxylin and eosin; × 175.

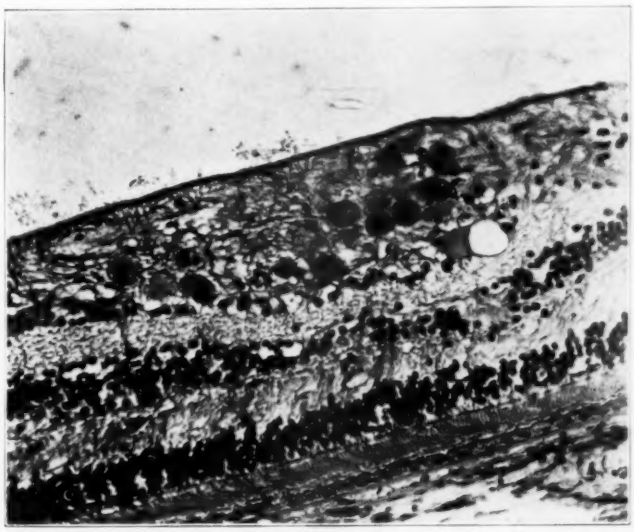

Fig. 15.—Collection of cytoid bodies in the layer of nerve fibers of the retina. Hematoxylin and eosin; × 150.

arteries the thickening was not, as a rule, due to excessive intimal changes but to gliosis around the vessel combined with slight medial hypertrophy. The internal elastic lamina was hypertrophied. The arterioles had thickened walls, due apparently to a medial rather than to an intimal change. The adventitia was surrounded by an excessive number of delicate fibrils which streamed off into the surrounding tissue. As in the brain, the capillaries showed a slight increase in the number of nuclei distributed along their walls. Surrounding the optic disk was a mass of homogeneous eosin-staining substance [26] between the retina and the choroid. Small collections of a similar substance were seen at various places in the retina; they were most numerous in the internuclear layer, but also were present in the inner molecular layer and even in the layer of ganglion cells. Large fresh hemorrhages were abundant, involving the layer

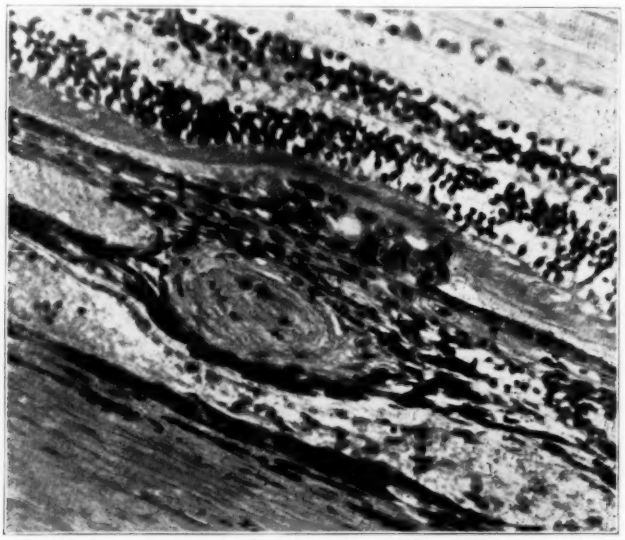

Fig. 16.—Small choroidal artery filled with large clear cells, probably due to proliferation and degeneration of the lining endothelial cells. Slight exudate between retina and choroid. Hematoxylin and eosin; ×150.

of nerve fibers, the layer of ganglion cells and the inner molecular layer, but they were also observed to penetrate all the layers of the retina, while minute hemorrhages were abundant in the internuclear layer and not so common elsewhere. There was evidence of glial proliferation throughout the retina; this was most marked in the region of the optic disk, where definite thickening was noted with an excessive number of glial cells as well as signs of edema, evidenced by widening of the spaces between the fibrils. Occasionally large masses of "cytoid bodies" (fig. 15) were encountered. In the internuclear layer, large

26. Older authors on this subject have used the word "exudate" to designate this substance. In view of the uncertainty in regard to its true nature or origin, we have been impelled to avoid this term in the histologic descriptions.

"foamy" cells were found (figs. 7 and 11). In some spots, they were present around the eosin-staining substances already mentioned; in others, they seemed to be alone. Some of the choroidal arteries (fig. 16) contained a type of cell similar to those just noted in the retina, but it is impossible to explain the presence of such cells within the lumina of arteries, and in all probability the foamy cells within the arteries have a different origin. They were probably proliferated, swollen and degenerating endothelial cells, and as a matter of fact various stages of the process of their formation were present in different vessels. It seems unlikely that these cells were the result of postmortem changes, although this source of origin has to be considered.

CASE 2 (case 80, table 7).—Emaciation (graded 2) was present, but edema and excess of fluid did not occur in any of the cavities of the body. The heart weighed 496 Gm.;[27] the cavities were not dilated, but there was definite thickening of the ventricular walls (left, 2 cm. and right, 0.5 cm.). The coronaries showed arteriosclerosis (graded 3), but they were not notably narrowed. Early bilateral embolic pneumonia was present in both lungs. The spleen, liver, pancreas, suprarenals and stomach did not show noteworthy lesions. In the cecum and ascending colon, acute ulceration apparently limited to the mucosa was present. The left kidney weighed 100 Gm. and the right, 106 Gm. After the capsules were stripped off, the kidneys had a granular surface with scars, some of which measured 4 mm. in diameter, and a few cysts 7 mm. in diameter. On section, the cortex was thin and the markings indistinct and irregular, while there was an increase in peripelvic fat. The right kidney contained a fresh infarct. The brain showed slight atrophy of the frontal convolutions, and the vessels of the circle of Willis were sclerosed (graded 3); the basilar arteries were dilated and also sclerosed (graded 3). On section of the brain, numerous small areas of hemorrhage, the largest of which was 1.5 cm. in diameter, were found in many places. There were also numerous areas of softening, some having formed cavities or cysts; these areas were smaller than those showing hemorrhage, the largest being 8 mm. in diameter.

On microscopic examination, the arteries of the kidney had definitely thickened walls due partly to hyperplasia of the intima, with hypertrophy and splitting up of the internal elastic lamina, and partly to hypertrophy of the medial muscular layer. There was also an increased amount of connective tissue in and around the adventitia. Many of the arterioles were almost completely obliterated, and some were occluded by intimal proliferation and definite hypertrophy of the media. In others the occlusion was by no means complete, but in all, thickening of the walls was marked. The capillaries showed little appreciable change, except those of the glomerular tufts, in which apparent cellular proliferation was present. Many glomeruli were more or less completely hyalinized, while in others the tuft was lobulated and there were some adhesions to the capsule. The capsule in some was thickened by an excess of fibrous tissue. Throughout the parenchyma interstitial fibrosis occurred. Some of the tubules were dilated to form small cysts. Here and there, small collections of lymphocytes were encountered.

The walls of the arteries in the spleen were much thicker than normal, and the intima was hyperplastic, while the internal elastic lamina was greatly hypertrophied and split up. The media was also excessively thickened by a fibrous hyaline type of tissue. Some of the arterioles were almost occluded by

27. The estimated normal weight of the heart for a patient of this age, height and weight was 200 Gm.

concentric hyperplasia of the intimal cells, and some were actually obstructed. The walls of some of these arterioles were hyalinized. Throughout the splenic pulp, moderate reticular fibrosis was present.

In the pancreas and liver there was definite thickening of the walls of the arterioles but much less in the walls of the arteries.

In the small intestine, the arteries and arterioles of the submucous and muscular coats showed thickening of their walls. In the cecum this thickening was more marked than in the small intestine and its submucosa was thick and edematous; the mucosa was absent in many places, and large numbers of polymorphonuclear leukocytes were present, as well as large masses of necrotic tissue.

There was a mild degree of sclerosis in the arteries and arterioles of the subarachnoid space, not comparable in any degree with those of the kidney or any other organ examined. In the brain parenchyma proper, the walls of most of the arterioles were definitely thickened, due mainly to intimal proliferation. Around some of the areas of softening, the arterioles were more or less obstructed by intimal proliferation. In some of these softened areas, large masses of blood pigment, which did not react to an iron stain, were present. With the blood pigment, large "scavenger" cells and edema were present.

In the eye, the lumina of the choroidal vessels were narrowed and their walls were thickened; this change was mainly the result of hyperplasia of the intima, but the media was also hypertrophied. Some of the arteries and arterioles were apparently completely occluded. In the lumina of certain arteries (fig. 16), large clear cells were abundant, intermingled with endothelial and connective tissue cells; one such artery showed canalization. In the retina the arterial change was much less marked than in the choroid, and the thickening was due mainly to hypertrophy of the media. The intima was only slightly changed. Numerous small areas of hemorrhage and masses of homogeneous, eosin-staining substance were present in the internuclear layer. Evidence of recent hemorrhage was occasionally seen in the layer of nerve fibers. Around some of these eosin-staining masses, large "foamy" cells might be seen. One large mass was present between the retina and the choroid at the entrance of one of the short posterior ciliary arteries. Here and there, proliferation of the retinal pigment epithelium also was present (fig. 14).

Case 3 (case 81, table 7).—Slight edema (graded 1) of the ankles was present; ascites was not present, but the left pleural cavity contained 1,000 cc. and the right, 50 cc. of clear straw-colored fluid; the pericardial cavity contained 150 cc. of similar fluid. The heart was greatly hypertrophied, weighing 870 Gm.[28] but it was not dilated; the left ventricular wall measured 2.2 cm. and the right, 0.6 cm. Slight myocardial fibrosis and only slight sclerosis (graded 1) of the coronary arteries were present. The spleen weighed 215 Gm. and the liver, 2,116 Gm. The colon contained multiple areas of petechial hemorrhage. The left kidney weighed 166 Gm., and on removal of the capsule the surface was coarsely granular and congested. On section, the cortex appeared narrow, but a few glomeruli could be seen grossly while the medullary markings were indistinct and irregular. There was a definite increase in the peripelvic fat. The right kidney was not examined. Arteriosclerosis (graded 2) of the aorta was noted. In the circle of Willis arteriosclerosis was pronounced (graded 3), and throughout the brain multiple small areas of softening were noted, but

28. The estimated normal weight of the heart of a patient of this age, height and weight was 310 Gm.

fresh hemorrhage was not evident. These softened areas were most abundant in the left lenticular nucleus and also near the left optic radiations, but they were also present throughout the cerebrum; they were not so abundant in the cerebellum, and none were noted in the pons or medulla oblongata. The posterior half of the right eye showed a considerable number of hemorrhagic areas, grayish exudates and apparent edema of the tissue around the optic disk.

Microscopically, the vessels of the kidneys showed profound change. In the arteries all the three coats of the vessels were involved, particularly the intima and media. The internal elastic lamina was also hypertrophied and thickened. In some vessels in the intima and between the intima and media, there was a considerable amount of mucoid material. The walls of the arterioles were thickened, and the lumina were obstructed more uniformly and completely than the arteries; this partial occlusion was mainly due to intimal hyperplasia, although some hypertrophy was also present in the media, and there was considerable fibrosis around the vessels. The capillaries appeared normal, except in the glomeruli. Throughout the kidney marked interstitial fibrosis was present, and many of the tubules were dilated and the epithelium flattened. In many of the lumina were homogeneous, colloid-like casts. In the midst of the fibrous tissue the remnants of numerous collapsed and shrunken tubules were noticed. Some glomeruli were hyalinized, a few had thickened capsules but the remainder seemed to be hypertrophied; there was also an increase in the number of nuclei in the tuft.

Mild reticular fibrosis was present throughout the spleen, and the walls of the vessels were thickened but not to such an extent as in the kidney. Intimal hyperplasia was seen, and the tissue immediately outside the intima was of a hyaline-like consistency; in the adventitia, there was moderate fibrosis.

Partial fatty replacement (graded 2) of the pancreatic pulp was seen. The walls of the arteries and arterioles were considerably thickened, while the capillaries were free from any appreciable change.

The arteries of the liver showed well marked hypertrophy of the media and hyperplasia of the intima. All the coats of the walls of the arterioles were thickened, but less so in the adventitia.

In the heart, muscle fibers were hypertrophic and were partially replaced by connective tissue. The media in its arteries was hypertrophied and the adventitia also, to a slight extent, while the intima showed only slight hyperplastic change. The arterioles were moderately affected, but the capillaries were free from any noticeable change.

In the aorta there was some calcification in the intima and media, but the most profound change was in the vasa vasorum, which in many places were almost occluded by the excessive hypertrophy of the media and hyperplasia of the intima. Around some of these vasa vasorum, there were collections of lymphocytes. The arterioles of the skeletal muscles showed hyperplasia of the intima as well as definite hypertrophy of the media and hypertrophy and splitting up of the internal elastic lamina.

The thyroid did not show signs of hyperactivity.

The intima in the basilar artery was thick, and areas of softening were present, while the media showed only mild hypertrophy. The lumina of the choroidal arteries and arterioles were almost obliterated, partly by hypertrophy of the media but more particularly by hyperplasia of the intimal endothelium. The internal elastic lamina was also hypertrophic and split. In the retina the vessels were like the vessels of the subarachnoid, and there was hypertrophy of the media but little intimal change. Some hypertrophy of the internal elastic

lamina also was present. The capillaries seemed to be free from fibrosis. Areas of hemorrhage were present but were not numerous. Evidence of larger recent hemorrhages was noted in the layers of nerve fibers and ganglion cells, while smaller and older hemorrhagic areas were present in the internuclear layer. Small masses of eosinophilic substance were also present in this layer, while a large mass was present in the layers of nerve fibers and ganglion cells.

The arteries and arterioles of the subarachnoid space showed hypertrophy of the medial coat but little change could be found in the intima or adventitia. In the brain parenchyma proper, the vascular changes found in the arteries were similar to those of the subarachnoid space. The arterioles of the brain tissue proper, on the other hand, showed proliferation of the intima and also hypertrophy of the media. The areas of softening were characterized by blood pigment, "scavenger cells," edema and necrosis.

Case 4 (case 37, table 7.)—Edema (graded 1) was present in the lower extremities, but other abnormal collections of fluid were not found in the upper extremities or cavities of the body. The heart weighed 400 Gm.;[29] the left ventricular wall was hypertrophied. A coronary sclerosis (graded 2) was present. In the right lung, there were bronchitis and early bronchopneumonia. Chronic passive congestion was found in the liver, but the spleen, pancreas, suprarenals and gastro-intestinal tract were without gross lesion. The kidneys weighed 135 Gm. each. Stripping the capsule revealed a fine granular surface. On section, the cut surface showed some pale areas. Arteriosclerosis of the aorta was graded 1+. Blood was diffusely present in the subarachnoid space, also in both lateral ventricles, especially in the left; this ventricular blood had evidently come from hemorrhage in the region of the left internal capsule, with destruction of tissue of the brain. Small areas of rust-colored softening, the largest of which was in the right thalamus, were present.

Microscopically, the arteries in the kidneys showed thickening of their walls; in the intima and the inner portion of the media, hyalinization was seen. The walls of the arterioles were thickened, and there was well marked intimal proliferation and hypertrophy of the media, so that the lumina in many places were almost occluded; in others, the lumen was obstructed and the walls hyalinized. Some glomeruli appeared to be hypertrophied, with lobulation of their tufts and partial hyalinization. In others, there was an increase in the number of nuclei in the capillaries while some capsules were thickened. An occasional cyst could be seen, but most of the tubules were normal. A few hyaline casts were seen in the loops of Henle. Interstitial fibrosis was also evident, and small collections of lymphocytes were seen.

Thickening of the walls of the coronary arteries was seen, but the arterioles showed a more advanced change. The myocardial fibers were slightly hypertrophied.

In the pancreas there was marked hyalinization of the islands of Langerhans, so that few normal islands remained. The arterioles of the pancreas, liver, spleen and suprarenals showed thickening and partial obstruction.

In the brain the walls of the arterioles showed hypertrophy of the media, which in some places was split and contained large fat cells; the intima was hyperplastic. In some of the perivascular spaces, collections of "scavenger" cells were present. In many of the arterioles, the media was hypertrophied and the intima was hyperplastic so that the lumen appeared almost occluded. This

29. The estimated normal weight of the heart of a person of this age, height and weight was 265 Gm.

change was present in all the sections examined. The capillaries did not show any appreciable change. Areas of softening were abundant, and many ganglion cells showed various stages of chromatolysis.

CASE 5 (case 32, table 7).—The body was obese (graded 3) and edema (graded 2) of the lower extremities was found. Ascites and hydrothorax on the right (1,000 cc) were present, but an estimation of the fluid in the pericardial cavity is not on record. The heart weighed 870 Gm.;[30] all the cavities were dilated and hypertrophied; the left ventricle was 2 cm. thick and the right, 0.6 cm. thick. Fibrosis (graded 3) of the myocardium was a marked feature on gross examination, and there seemed to be incompetence of the mitral valve, owing to stretching of the ring, which measured 11 cm. Mild sclerosis (graded 1) of the coronaries was present. The spleen and liver were larger than normal. Gross lesions were not observed in the gastro-intestinal tract or the pancreas. The left kidney weighed 190 Gm., and the surface was roughly granular after the capsule had been stripped. On section, the cortex was thin and the markings were indistinct. The right kidney was similar to the left.

Microscopically, the arteries of the kidneys showed hypertrophy of the media; the intima was hyperplastic, and there was hypertrophy and splitting up of the internal elastic lamina. An excessive amount of fibrous tissue was present in the adventitia and also immediately near it. The arterioles were more involved than the arteries; the media was hypertrophic, but the hyperplastic change of the intima was the outstanding feature in many vessels; in others it was the medial change. In some arterioles these processes had advanced to the point of complete occlusion of the lumen. Many glomeruli were completely hyalinized, while others were only partly destroyed. In a large number the capsules were thickened. Few tubules were dilated, but many were completely collapsed, shrunken or disintegrated.

Slight central necrosis was present in the liver, and in this organ the walls of the arteries and arterioles were thickened.

In the heart the media of the coronary arteries was hypertrophied; the intima did not show appreciable change, but there was increased fibrosis in and around the adventitia. Certain arterioles were almost occluded, but others were patent; around the former, there was advanced fibrosis. Some fibers were hypertrophied, and many were seen to contain minute droplets of fat, especially around the nuclei, but also elsewhere within the fiber.

CASE 6 (case 26, table 7).—Edema was present over the forearms and backs of the hands (graded 2) and ankles (graded 1), but there was not an excess of fluid in any of the cavities of the body. The heart weighed 715 Gm.,[31] and showed hypertrophy of the ventricular walls, the left being 2 cm. thick and the right, 0.6 cm. thick. The myocardium did not show gross fibrosis. The coronaries were sclerosed (graded 2). Slight edema and congestion were present at the base of both lungs. The spleen, liver, pancreas, suprarenals and gastro-intestinal tract did not present notable lesions. The kidneys weighed 97 Gm. each, and the surfaces were granular, with many small whitish nodules scattered over the surface as well as a few small cysts containing clear yellowish fluid. On section, the cortexes were thinner than normal, being 5 mm. thick, and

30. The estimated normal weight of the heart of a person of this age, height and weight was 370 Gm.

31. The estimated normal weight of the heart of a person of this age, height and weight was 270 Gm.

the medullary markings were irregular but fairly distinct. Arteriosclerosis of the aorta was graded 2, and a few discrete areas of calcification were present in the abdominal portion. Histologically, the arteries of the kidneys showed marked change in the normal ratio of blood vessel wall to lumen; the latter was constricted and the former thickened, due to hypertrophy of the media and internal elastic lamina, which was split and contained the hyperplastic intima within its meshes. In the adventitia, there was an increased amount of connective tissue which was also present around the vessel. The arterioles showed changes similar in degree. The capillaries were free from any change in their walls, except in the glomerular tufts. Some glomeruli were hyalinized, but the majority appeared to be increased in size; in some there appeared to be an increase in the number of nuclei in the capillaries of the tufts. Many tubules were dilated and contained hyaline or epithelial casts. Interstitial fibrosis was present, while collections of lymphocytes were rare. The walls of the coronary vessels were not thickened, but the myocardial fibers were definitely hypertrophied. In the pancreas, liver, spleen and lungs there were hypertrophic vascular lesions involving the arteries and arterioles, but again the capillaries seemed to be free.

CASE 7 (case 45, table 7).—The necropsy in this case was performed elsewhere, and we received only portions of the kidneys for microscopic examination. Sclerosis was present in most of the smaller arteries and arterioles, while others were less affected. Some glomeruli were completely hyalinized; others were only partially hyalinized, a small portion or even half of a glomerulus being destroyed in this way. Most of the glomeruli showed apparent hypertrophy and an increase in the number of nuclei in the capillary tufts, but in a few the capsule was thick. Interstitial fibrosis was present throughout the kidney. In certain areas, some of the tubules were dilated and filled with hyaline-like casts, but in other areas only a few epithelial cells remained in the increased fibrous tissue to indicate the presence of destroyed tubules. In a considerable number of tubules, the epithelium was well preserved.

BACTERIOPHAGY IN URINARY INFECTIONS FOLLOWING THE ADMINISTRATION OF THE BACTERIOPHAGE THERAPEUTICALLY *

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It has been shown that sewage filtrate contains lytic principle of marked activity for most of the gram-negative bacilli found in cases of urinary infections.[1] Of seventy-five consecutive cases of urinary infections which I have studied up to the present time, sewage filtrate has lyzed 90 per cent of the strains of bacilli isolated from the catheterized specimens of urine. The activity of the sewage filtrate is marked, either in the first passage or after only one or two passages. A complete report of this phase of the subject will be made after the series has been extended.

Because of the ease with which the lytic principle could be obtained from sewage filtrate for these organisms, and the fact that in the past the chief obstacle to the use of the bacteriophage in urinary infections has been the lack of potent bacteriophage to many of the causative bacilli, the situation appeared hopeful for the treatment of the patients with sewage filtrate. A small number of patients, twelve in all, have been treated recently, and the processes of bacteriophagy have been followed through frequent cultures of urine and examinations of urine filtrates. Certain observations have been made which have influenced the mode of treatment, and which throw some light on bacteriophagy in the human body. There is a striking paucity of such observations in the literature, and even the few reported are in conflict, so that there is reason for presenting in some detail such a small number of cases at this time. The clinical and therapeutic phases will not be given here, except to say that the cases were chronic, and in most instances the patients had been treated by other methods.

The chief observations that have been reported on the fate of injected bacteriophage have been made in two types of studies: (1) studies of the viscera at various intervals when bacteriophage was injected into normal, uninfected animals, (2) studies of animals after the simultaneous administration of bacteriophage and susceptible organisms.

Experiments of the former sort are summarized in d'Herelle's book, "The Bacteriophage and Its Behavior." [2] There is general agreement

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1. Cowie, D. M.: Observations on the Bacteriophage, Ann. Clin. Med. **5**:57 (July) 1926. Caldwell, Janet: Sewage Filtrate as a Source of Bacteriophage, J. Infect. Dis. **4**:575 (May) 1927.

2. D'Herelle, F.: The Bacteriophage and Its Behavior, Baltimore, Williams & Wilkins Company, 1926, p. 381.

that the bacteriophage does not persist in normal organs; it disappears from most of them as early as three hours after injections, and from all of them after twenty-four hours.

Arnold and Weiss [3] have used the second method in testing the efficiency of their protein-free filtrates. In these experiments, they injected lethal doses of Shiga dysentery or typhoid bacilli simultaneously or at short intervals with the bacteriophage. They did not produce experimental disease comparable to the pathologic conditions in man. They believe from their observations that bacteriophage does not increase in vivo as in vitro, and that, therefore, a large proportion of bacteriophage is necessary (comparable to the proportion which prevents clouding of tubes in vitro) to effect cure of lethal doses of *B. typhosus*. The author's experience and that of others in cases of urinary infections in which natural disease exists is at variance with such conclusions.

Schumm and Cooke [4] have reported the constant recovery of homologous bacteriophage administered in staphylococcus infections of the nasal sinuses. They do not report any diminution in organisms or pus, nor any acquisition of resistance of the culture in association with the bacteriophage. The following observations confirm the fact that the bacteriophage can be recovered from the products of the lesions and is constantly present when cure is not effected, but it has always been possible to demonstrate readily resistance of the culture to the bacteriophage.

The bacteriophage used in treatment was isolated from sewage filtrate in the usual way and was built up on the patient's organism by a few serial passages until it gave maximum or marked lysis. It was always concentrated by adding an entire agar slant suspension to 20 or 25 cc. of the filtrate and incubating until lysis occurred (from eight to eighteen hours). This concentrated filtrate was given by subcutaneous injections and lavage of the bladder, usually daily or every other day for from three to six injections.

DIAGNOSIS OF ORGANISMS TREATED

In classifying the organisms isolated from the catheterized specimens of urine, the usual culture mediums were used: gelatin, Russell's medium, dextrose and lactose broth, litmus milk and citrate agar. *B. coli* was present in pure culture in eight cases; in three cases *B. pyocyaneus*, associated with a streptococcus in two. In one case the

3. Arnold, Lloyd; and Weiss, Emil: Prophylactic and Therapeutic Possibilities of the Twort-d'Herelle's Bacteriophage, J. Lab. & Clin. Med. **12**:20 (Oct.) 1926.

4. Schumm, Elsie, and Cooke, Robt.: Incidence and Therapeutic Value of Staphylococcus Bacteriophage in Antrum Infections, J. Infect. Dis. **39**:424 (Nov.) 1926.

organism had the culture characteristics of *B. pyocyaneus*, and during treatment it developed a diffuse, pale lavender pigment; therefore it was considered to be an atypical *B. pyocyaneus*.

Dissociation phenomena were present in all the cultures, and by the use of the artificial colony method, the stage of dissociation as elucidated by Hadley [5] could be recognized. No difference which correlated with any one stage of the dissociation cycle could be detected in the ease with which these organisms could be lyzed by sewage filtrate. This has also been true of the large group of urinary organisms now being studied.

BACTERIOPHAGE IN URINE

Frequency of Native Bacteriophage in Patient's Urine.—Before beginning to treat the patient, a urine filtrate was obtained. This was

TABLE 1.—*Results of Examinations of the Urine of Patients Treated with Homologous Bacteriophage*

Serial No.	Diagnosis	Bacteriophage in Urine		Time of Appearance	Persistence	Urine Culture	Time to Become Sterile	Resistance Developed
		Before	After					
13U	B. coli	—	—	.....	.....	Sterile	3 days	—
18U	B. pyocyaneus	—	—	.....	.....	Sterile	2-7 days	—
34U	B. coli	—	—	.....	.....	Sterile	By 10th day	—
74U	B. coli	—	+ once	48 hours	Gone in 48 hours	Sterile	5 days	—
D	B. coli	—	+	1½ hours	31 days	Sterile	36 hours	—
1U	B. pyocyaneus	+	+	Not followed		+	.....	+
9U	B. coli	—	+	3 days	4 mo. +	+	.....	+
17U	B. pyocyaneus	+	+	3 days	1 mo. twice	+	.....	+ twice
21U	Atypical B. pyocyaneus	—	— suicide culture	By 11th day	1 m.o.	+	.....	+
36U	B. coli	—	+	2-5 days	Died	+	.....	+
64U	B. coli	—	+	2 hours	36 hours	+	.....	
				Treatment was not completed				
67U	B. coli	—	+	6 hours	6 days +	+	.....	+

examined for the presence of a bacteriophage by testing through five passages against a stock *B. dysenteriae, B. coli* and the patient's own organism. I am convinced that this method does not give the true notion of the frequency of bacteriophage in the urines, but it is about as extensive a method as is practical.

Typical bacteriophage phenomena (plaques and lysis) were obtained from the urine filtrates of two patients, both cases in which *B. pyocyaneus* was present. In large series of urines tested,[6] the frequency of native bacteriophage is from 20 to 25 per cent.

Recovery of Bacteriophage Administered.—Bacteriophage could be recovered in all urines following treatment except those which became sterile (table 1). Of the latter cases, 74U, showed the bacteriophage on

5. Hadley, Philip: Microbic Dissociation, J. Infect. Dis. **40**:1 (Jan.) 1927

6. Larkum, N. W.: Bacteriophagy in Urinary Infections, J. Bact. **12**:203 (Sept.) 1926.

only one examination, but D showed it persistently. D is an exceptional case; it is the only case in which the urine became sterile and in which the bacteriophage was strong and constant in the urine, so that a more detailed account of it is necessary to explain the apparent inconsistency. The patient had a puerperal infection in which a hemolytic *B. coli* was isolated from the blood. Besides pyelitis, colitis was present. The fact that the bacteriophage persisted in the sterile urine is, I believe, evidence that lesions due to this bacterium were still present in the body. The urine of D became sterile in thirty-six hours after beginning treatment, but the urine continued to give maximum lytic action as already stated, so that I was not surprised when a few colonies returned at the end of five days, accompanied by a return of symptoms. The few colonies persisted for weeks, always in the presence of a strong bacteriophage. These colonies always gave typical suicide cultures, that is, they could be cultivated on agar for a few generations, but finally gave ragged growth and then sterile slants, while in broth either they failed to grow or the slightly cloudy cultures cleared early. Thus D illustrates a typical mixed culture of a bacteriophage of maximum virulence and a susceptible bacterium, a condition described in vitro by d'Herelle.

The bacteriophage recovered in the urine was always similar in strength to the one administered but could not always have been demonstrated unless the original culture had been available, for the bacteriophage strains for the heterogeneous colon and allied organisms are specific and limited in their range of activity, and the organisms in contact with them become modified and resistant early.

Time of Appearance of Bacteriophage in Urine.—The time of appearance of the bacteriophage in the urine during treatment varied. In some cases it could not be recovered before the third day, while in other cases it appeared in a few hours. To try to determine how early the bacteriophage might appear, three patients were given the first subcutaneous injection from one to three hours before the first lavage of the bladder. The urine was drawn off before the filtrate was instilled into the bladder; cultures were made immediately, and the filtrate was studied. In one of these cases, D, many plaques were present in the agar plate culture one and one-half hours after giving 2 cc. subcutaneously, and the urine filtrate was as strong as the concentrated bacteriophage administered.

In a second case, 64U, a similar positive filtrate was obtained two hours after the first injection. In a third case, 67U, the urine obtained in thirty minutes was negative, but when the urine was drawn off six hours later, its filtrate contained the bacteriophage.

Thus it appears that the bacteriophage, when administered subcutaneously, may appear in the urine of infected patients within two

hours. It can be recovered constantly in cases in which the organisms persist, but when the urine becomes sterile, it is not present or is transitory. This indicates that the decisive action of bacteriophage on the organism occurs in the lesions, and when the lytic action is promptly successful, the bacteriophage cannot persist. This is consistent with bacteriophage action in vitro where its sole medium for growth is the living bacterium. The situation just described was really the opposite of what was expected, for it seems at first inconsistent that the presence

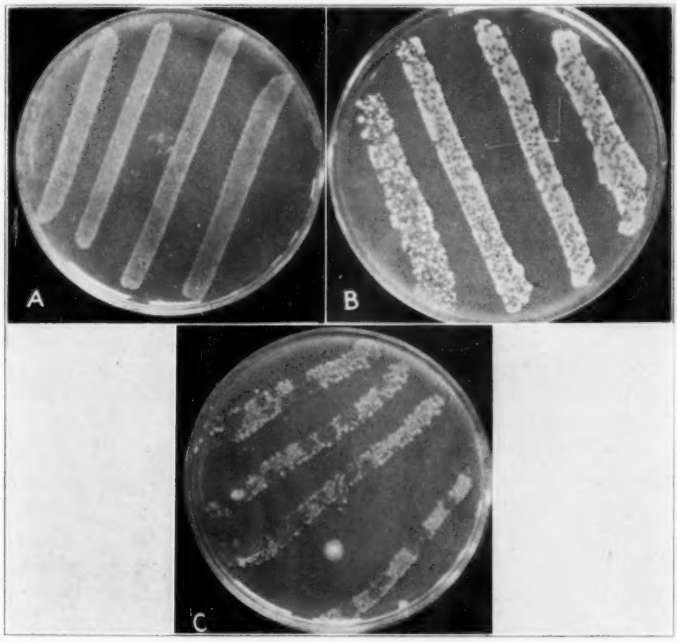

Fig. 1.—Evidence of lysis in cultures during treatment. *A* indicates a culture of urine just before treatment was begun, a typical normal growth. *B* (case D) indicates a culture of urine taken one and one-half hours after 2 cc. of bacteriophage was given subcutaneously; note the plaques. Thirty-six hours later cultures were sterile. *C* (case 74U) shows a culture taken after forty-eight hours of treatment. Sterile cultures were obtained after the fifth day.

of the bacteriophage in the urine is unfavorable for the ultimate cure of the patient, but on closer thought it is really what should happen if the action of the bacteriophage is similar in vivo to results in the test tube. In the latter, the action of the bacteriophage, if it prevents the development of secondary cultures, must be violent and early; any action less than this can produce mixed cultures of bacteriophage and

organisms representing all degrees and stages of equilibrium, some of which persist through many transfers. That this is what happens in the body and explains the simultaneous presence of the bacteriophage and the organism in the urine, will be brought out in the following description of the changes in cultures during the administration of the bacteriophage.

Persistence of Bacteriophage in Patient's Urine.—When the organisms persisted in the urine, the bacteriophage remained for some time and in certain cases which were followed could be demonstrated for months after treatment was discontinued. Naturally, the data here is incomplete, as the work is too recent to have allowed a long period of observation. In three instances, twice in 17U and once in 24U, the bacteriophage disappeared after about one month, and the organism was found to be reverting to its original cultural characteristics.

The persistence of the bacteriophage in the urine for such periods can scarcely be interpreted in any other way than as evidence of its increase in the body when natural lesions and organisms are present.

EFFECT OF BACTERIOPHAGE ON ORGANISM

One of the most striking results of administration of bacteriophage is the effect produced on the organism. The modification in growth or pigment characteristics were so striking that a systematic study of the cultures during treatment was undertaken early. Observations were made on the cultural and growth characteristics and on the susceptibility to the bacteriophage administered and to sewage filtrate.

The artificial colony method is an excellent way to note size, shape, density, thickness, pigment production and dissociation phenomena of a culture. Freshly poured and hardened agar plates are inoculated by stabbing the center with a straight platinum wire which has previously been carried over a twenty-four hour agar slant culture. The central colonies are measured and observed at regular intervals for any length of time, usually ten days.

The results of these studies have been summarized in table 2. In all cases in which the urine was not sterilized, and in some of the latter cases before sterilization, the organism was modified. The change occurred promptly, in from fifty-six hours to eleven days, and usually persisted for some weeks, with reversion after the bacteriophage disappeared from the urine. The changes did not affect the cultural characteristics of the organism in any case; the diagnosis was, therefore, the same. The organism as modified was always resistant to the bacteriophage administered, but could be lyzed by sewage filtrate with but one exception. These tests were carried out for one passage only, and the new culture was not studied in poured plates to determine its various

constituents of sensitive and resistant colonies. Doubtless the modified cultures represent such composite cultures, or the bacteriophage could not exist in its presence.

As to modification of growth characteristics, these were not consistent either in degree or in type of change produced. No change could be noted in two instances, 9U and 67U; resistance was the only sign of modification in these cultures. In this connection 9U proved to be an unusual organism, for it always developed early and perfect secondary cultures to any bacteriophage found for it so that, although lysis was

TABLE 2.—*Modification of Urinary Cultures During Treatment with Homologous Bacteriophage*

Serial No.	Original Characters	Modified Characters	Modified Culture Tested with: Treatment Bacteriophage	Modified Culture Tested with: Sewage Filtrate	Time for Modification	Tendency to Reversion
1U	Green pyocyaneus	Gave amber colonies	R	Lyzed	3 days	
9U	11 mm.; smooth	11 mm.; smooth	R	Lyzed	5 days	Still resistant after 4 mo.; bacteriophage in urine
17U	28 and 33 mm.; green	13 mm.; colorless	R	Lyzed	7 days	Gradually in 2 mo.; bacteriophage disappeared
17U†	13 mm.; yellow green	5 mm.; colorless	R	Not lyzed	3 days	Gradually; bacteriophage disappeared
24U	45 mm.; transparent	1 mm.; suicide	R	Lyzed	Within 10 days	Gradually in 1 mo.; no longer suicide
36U	14 mm.; round	19 mm.; irregular	R	Lyzed	5 days	Patient died
67U	9 mm.; irregular	11 mm.; round	R	Lyzed	56 hours	Sterile 8 weeks later
74U	13 and 21 mm.; round	Suicide	*	*	6 days	In 7 days; no bacteriophage in urine
74U†	13 mm.; round	30 mm.; very irregular	Lyzed	Lyzed	4 days	Sterile on eighth day
D	55 mm.; irregular	2 mm.; suicide	*	*	By 11th day	Still suicide 31 days later

* Could not be tested adequately due to spontaneous lysis of broth cultures.
† Second treatment after reversion.

maximum up to eight hours, in eighteen hours no difference from the controls could be detected. Patient 9U was treated twice without effect on the number of organisms or on the patient; from this experience the conclusion seems warranted that it is useless to administer a bacteriophage which cannot show some degree of permanent lysis in vitro.

The most frequent change in growth characteristics was the production of smaller colonies, sometimes even suicide cultures. With *B. pyocyaneus,* pigment production was lost, and the spreading tendency, transparency and the production of luster areas were lost, so that the culture gave a compact, regular, opaque colony. In two cases, the change revealed itself as a greater growth tendency with a larger colony usually spreading from one point to form an irregular shape.

Because the cultural characteristics remained the same and because the organism in a few instances was seen to revert to its original nature, these changes are considered to be true modifications and not a substitution of one infecting organism by another.

In conclusion, it can be stated that during the treatment of patients with urinary infections by a bacteriophage built up on the causative organism, either the urine is sterilized or the organism is modified, at least in its susceptibility to that bacteriophage and usually, more profoundly, in its growth characteristics.

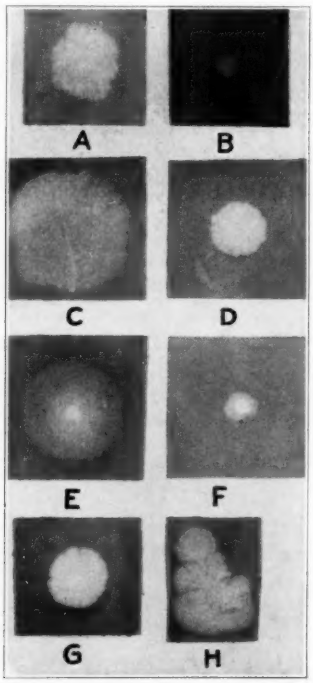

Fig. 2.—Growth modification in cultures following treatment. *A* and *B* (case 24U) indicate growths before and after treatment. The small colony is a typical "suicide" culture in broth. *C* (case 17U) shows the original culture, large colony, green pigment, no bacteriophage in urine; *D*, the culture after treatment, small colony, no pigment, more opaque growth, resistant, bacteriophage in urine; *E*, the culture two months later showing partial reversion, colony larger, yellowish pigment, no bacteriophage in urine; *F*, the culture after second treatment, small colony, no pigment, resistant, bacteriophage in urine; *G* and *H* (case 36U), before and after treatment; note the greater growth activity following treatment. This culture is now resistant and the bacteriophage is present in patient's urine in maximum strength.

From these observations it is clear that the chief problem in the use of the bacteriophage in urinary infections is that of the ready adaptability of the organisms usually found in these cases so that they become resistant to the bacteriophage administered. The hope in this connection is the fact that resistance is individual—a resistance to only that one bacteriophage strain—and that the modified organism can be as readily lyzed by a rich source of bacteriophage, sewage filtrate, as if it had not been in contact with a bacteriophage.

The prospect, therefore, appears hopeful, but to combat the natural difficulty certain precautions seem essential. The bacteriophage used should not allow the early development of secondary cultures. It should be prepared and administered promptly, at frequent intervals and in adequate quantities locally so as to lyze the main bulk of organisms quickly, thus preventing the modification which results in resistance. Cultures should be watched and if necessary relyzed by sewage filtrate, and the second bacteriophage should be administered.

CONGENITAL MALFORMATIONS OF THE GALLBLADDER

REPORT OF THREE CASES OBSERVED BY CHOLECYSTOGRAPHY

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Any method of precision used in the diagnosis of disease has possibilities far surpassing its immediate application. The physician, however, is chiefly concerned with its immediate value to his patient. While this attitude is entirely commendable, the fact that a positive diagnostic method may become an instrument of investigation in the hands of the clinician should, nevertheless, be recognized. The application of radiology to the stomach has modified the conception of the anatomy of this organ. Radiology has added to the knowledge of gastric physiology, and has enabled physicians to observe the reactions of the stomach to drugs.[1] The clinician has thus been enabled to add considerably to the knowledge of the anatomy and physiology of the stomach and of the modifications of it caused by drugs. Radiology has, therefore, increased his usefulness to medicine, and rendered him less dependent on the anatomist and on the experimenter with laboratory animals.

When cholecystography was introduced in medicine,[2] the attention of physicians was directed almost entirely to its clinical value. So valuable a method, however, was predestined to wider usefulness. A method giving accurate information about the size, shape and position of the gallbladder and about its power of concentration and ability to empty its contents obviously will give valuable knowledge concerning its anatomy and physiology and concerning its response to drugs. Indeed, the question whether the gallbladder is a passive organ, or whether it empties its contents by the contraction of its walls, has already been solved by this method. Whitaker,[3] by experiments on animals, and Levine,[4] by observations on man, demonstrated contractions of the gallbladder by means of cholecystography. Clinicians should therefore be mindful of the opportunities for investigation inherent in positive diagnostic methods.

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1. Assmann: Klin. Röntgendiagnostik d. Inneren Erkrankungen, ed. 3, Leipsic, F. C. W. Vogel, 1924, p. 400.

2. Graham, E. H., and Cole, W. H.: Roentgenologic Examination of Gallbladder: New Method Utilizing Intravenous Injection of Tetratromphenolphthalein, J. A. M. A. **82**:613 (Feb. 23) 1924.

3. Whitaker, L. R.: Am. J. Physiol. **78**:411, 1926; Diagnosis of Gallbladder Disease, J. A. M. A. **88**:1791 (June 4) 1927.

4. Levine, S.: Contractions of Gallbladder Seen in Man, Arch. Int. Med. **40**:420 (Oct.) 1927.

Congenital anomalies of the gallbladder are frequent in animals, particularly in sheep, cattle and cats. They are said to be rare in man (Konjetzny [5]). Huber [6] reported a case of congenital absence of the gallbladder "with preternatural enlargement of the hepatic duct." Double gallbladders were described by Sherren,[7] Braun [8] and Nichols.[9] Diverticula of the gallbladder were reported by Courvoisier,[10] by Staub [11] and by Sebening and Schöndube.[12] In the case of the last named authors, the diverticulum was large enough to interfere with the emptying of the stomach. Of the twenty-eight cases mentioned by Courvoisier, eighteeen patients had gallstones. A traction diverticulum was present only once. Hour-glass gallbladders were reported by Courvoisier, Hartmann,[13] Malcolm,[14] Morton [15] and Toida.[16] Malformations of the extrahepatic ducts are rather more frequent (Courvoisier,[10], Konjetzny,[5] Buzik,[17] Meyenburg,[18] Böhm,[19] Budde,[20] Dreesman [21]). It is probable that cholecystography will add an interesting chapter to the study of anomalies of the gallbladder. With the exception of the case of Nichols,[9] anomalies thus far reported have been observed only when the abdomen has been opened by either the surgeon or the pathologist. By means of cholecystography, however, physicians are able to study this condition in the living, ambulant patient, in whom this observation may be made accidentally. It is significant that in a rather small private practice, this method revealed three interesting anomalous gallbladders within a few months.

REPORT OF CASES

CASE 1.—*Hour-glass gallbladder.*

Mrs. S. S., aged 23, married eleven months, had never been pregnant. The history of menstruation was normal. Six months previous to her present

5. Konjetzny: Ergenbn. d. allg. Pathol. u. path. Anat. **14**²:712, 1910.
6. Huber: Philosophic Transactions, (abridged), London, 1744-1749, p. 649.
7. Sherren: Ann. Surg. **54**:204, 1911.
8. Braun: Zentralbl. f. Chir. **53**:1055, 1926.
9. Nichols: Radiology **6**:255, 1926.
10. Courvoisier: Casuistisch-statistische Beitrage zur Pathologie und Chirurgie des Gallenwege, Leipsic, F. C. W. Vogel, 1890, p. 12.
11. Staub: Cor.-Bl. f. schweiz. Aerzte **26**:15, 1896.
12. Sebening and Schöndube: Arch. f. klin. Chir. **137**:308, 1925.
13. Hartmann: Bull. Soc. anat. de Paris **66**:480, 1891.
14. Malcolm: Proc. Roy. Soc. Med., Surgical Section, part 3 **1**:93, 1907-1908.
15. Morton: Brit. M. J. **2**:1697, 1908.
16. Toida: Arch. f. klin. Chir. **100**:1188, 1913.
17. Buzik: Arch. f. Verdauungskr. **22**:370, 1916.
18. Meyenburg: Virchows Arch. f. path. Anat. **221**:352, 1916.
19. Böhm: Ztschr. f. ang. Anat. **1**:105, 1913-1914.
20. Budde: Deutsche Ztschr. f. Chir. **185**:339, 1925; München. med. Wchnschr. **72**:848, 1925.
21. Dreesman: Deutsche Ztschr. f. Chir. **92**:401, 1908.

illness she was in an automobile accident in which she sustained minor injuries of the right shoulder and right arm. The right ear drum was perforated during this accident. The patient came to my office on May 3, 1927, with the following history: The tonsils had been removed seven years before. One week after tonsillectomy, she had had an attack of acute abdominal pain which had been diagnosed as acute appendicitis. Operation had not been performed. Four weeks ago she had had diffuse abdominal pain which settled in the lower right quadrant of the abdomen. The pain still persisted in a milder form. It was cramplike in character and was not relieved by food. Occasional heartburn,

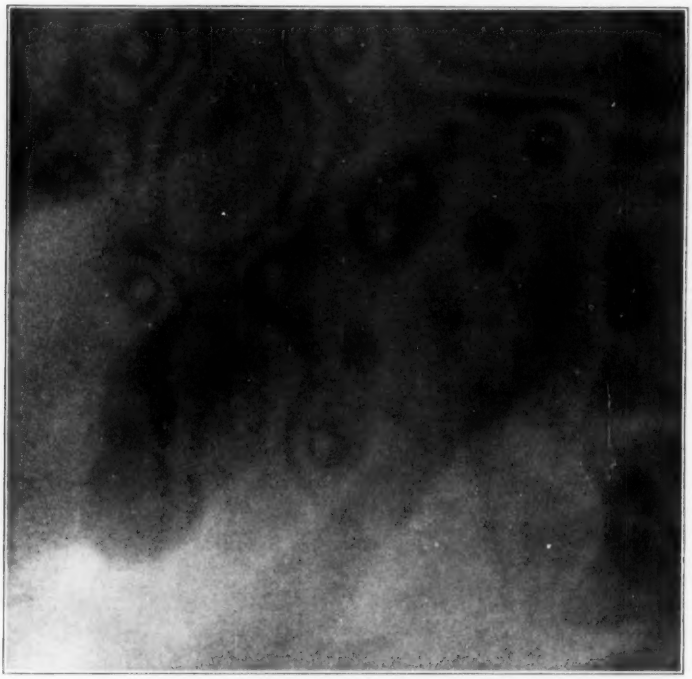

Fig. 1 (case 1).—Cholecystogram of hour-glass gallbladder.

independent of meals, was not relieved by food but was relieved by sodium bicarbonate. The patient belched considerably. Occasional pressure was present in the epigastrium. She did not vomit during or between attacks of pain. The bowels moved once in from one to two days without the aid of a cathartic.

The results of a physical examination were negative, with the exception of the observation of tenderness in the lower right quadrant of the abdomen. The blood count and blood chemistry did not reveal anything abnormal. The icteric index was 9.5 (normal from 4 to 6). One hour after an Ewald test meal, the hydrochloric acid was 11, and the total acidity was 30. The urine and stool were normal. The blood Wassermann reaction was negative. Proctoscopic examination showed a normal rectum and sigmoid. The fluoroscopic

and roentgenographic examinations of the gastro-intestinal tract did not reveal any abnormalities, with the exception of constant tenderness in the lower right quadrant of the abdomen. The appendix was not visualized.

Fourteen hours after administration of the dye (tetraiodophenolphthalein sodium) by mouth, roentgenograms showed the gallbladder distinctly. At the junction of its middle and lower thirds, a circular constriction divided it into a wider upper and a narrower lower portion (fig. 1). Ten minutes after

Fig. 2 (case 1).—Hour-glass gallbladder about half its former size ten minutes after the ingestion of a fat meal. Proportionately, the lower cavity is diminished in size, even more than the upper.

the injection of a fat meal, the gallbladder was about half its former size (fig. 2). Proportionately, the lower cavity had diminished in size even more than the upper. Two and a half hours after the administration of the dye, only a small speck of it was seen in the gallbladder (fig. 3).

Morton's [15] case did not show any evidence of cholecystitis, although stones were present in both the upper and the lower cavities, while in

Toida's [16] case there was extensive inflammation of the lower portion of the gallbladder, but stones were not found. Both considered their cases as congenital in origin. Malcolm [14] and Hartmann [13] explained the hour-glass shape of the gallbladders in their cases by cicatricial con-

Fig. 3 (case 1).—Two and a half hours after the ingestion of a fat meal, only a small speck of dye is seen in the gallbladder.

traction secondary to inflammation. In all of the fifteen cases compiled by Courvoisier,[10] examination revealed either stones or definite traces of their presence at some former time.

In the case here reported, the origin of the condition is not entirely clear. The right-sided abdominal pain, pressure in the epigastrium,

belching and hypochlorhydria, together with the high icteric index (9.5), favor the diagnosis of cholecystitis, while the fact that the gallbladder concentrated and emptied in a normal manner speaks against this assumption. On the other hand, the presence of cholecystitis does not rule out the congenital nature of its anomalous form. Inflammation and stone formation may develop as a result of the abnormal shape of the gallbladder, which interferes with its emptying. In this case, however, we were confronted by the fact that the gallbladder concentrated and emptied normally. Spasm can be ruled out, since the musculature of the gallbladder was arranged irregularly and a circular layer was not present (Aschoff and Bacmeister,[22] Stöhr-Möllendorf,[23] Lütkens [24]). Whether there was any relation between the patient's recent accident and the hour-glass shape of the gallbladder is entirely problematic. Whatever pathologic conditions may be superimposed, the congenital origin of this hour-glass gallbladder is plausible.

CASE 2.—*Gallbladder resembling a "Phrygian cap."*

Mrs. F. L., aged 26, married for a period of three and a half years, had never been pregnant. Menstruation began at the age of 12 and occurred every twenty-eight days, lasting three days. Three years previous to her present illness, she stopped menstruating for six months; since then menstruation had been normal. During the last two years, she had suffered from weakness, excessive perspiration, palpitation and diarrhea (from four to five movements a day). Six months ago, she experienced severe pain at the right costovertebral angle accompanied by dysuria and vomiting. Eleven weeks ago, and again seven weeks ago, she was suddenly seized with cramps in the right lower quadrant of the abdomen. She did not vomit, but diarrhea persisted during these attacks.

The pulse rate was 120. The blood pressure was 98 systolic and 38 diastolic. The temperature was 99.4 F. There was marked tremor. A large goiter and exophthalmos were also present. Graefe's sign was positive. Thrill was felt, and bruit was heard over the thyroid. Kyphosis of the thoracic spine was evident. A systolic murmur was heard over the precordium, and was transmitted to the vessels of the neck. Tenderness was marked over the upper left dorsal region and over the lower part of the precordium. The right lower quadrant of the abdomen was tender and rigid. Dermographia was marked. A tender mass was felt in the right vaginal fornix.

The basal metabolism was +43. Specimens of urine showed a trace of albumin and a few red and white blood cells. The blood count and blood chemistry did not reveal any abnormalities. The blood Wassermann reaction was negative. Fluoroscopic and roentgenographic examination of the gastrointestinal tract showed that the stomach was extended down one and a half

22. Aschoff and Bacmeister: Die Cholelithiasis, Jena, Gustav Fischer, 1909, p. 11.

23. Stöhr-Möllendorf: Lehrbuch der Histologie, ed 20, Jena, Gustav Fischer, 1924, p. 315.

24. Lütkens: Aufbau und Funktion der extrahepatischen Gallenwege, Leipsic, F. C. W. Vogel, 1926, p. 77.

handbreadths below the crest of the ilium; the incisura angularis was two finger-breadths below. Tenderness was present to the right of the umbilicus. After four hours, the stomach was empty, and after twenty-four hours, the entire gastro-intestinal tract was empty, but the appendix was filled. It was irregular in outline and beaded.

Fig. 4 (case 2).—Cholecystogram of gallbladder resembling a "Phrygian cap." Note the notch between the body and the ampulla.

Fourteen hours after the administration of the dye (tetraiodophenolphthalein sodium) by mouth, roentgenograms showed the gallbladder clearly (fig. 4). Its lower pole was bent upward and toward the spine. Two hours after the ingestion of a fat meal, the gallbladder was empty.

In 1916, Bartel [25] described three anomalous gallbladders observed at autopsy. In each case the lower pole was bent upward in such a way as to suggest a "Phrygian cap." One was that of a girl, aged 15, with diabetes mellitus; the second, that of a women, aged 30, with syphilis of the liver and of the aorta, and the third that of a woman, aged 41, with tuberculosis of the lungs and peritoneum. All three had cholesterol stones in the gallbladder. Two years later,[26] this author reported forty more autopsies in which the same or similar anomalies in the shape of the gallbladder were observed. Six of his forty-three patients had pure cholesterol stones, and one had an inflammatory stone. From a study of the clinical histories and pathologic observations in these cases, he came to the conclusion that such a gallbladder is a sign of constitutional inferiority. It is often associated with lymphatism, status thymico-lymphaticus, hernia, genital hypoplasia and a narrow aorta, and it predisposes to tuberculosis, syphilis, cystic ovaries and adenomatous goiter.

The gallbladder of the patient in the case under consideration seems to answer to Bartel's description, although his articles do not contain any photographs. It is significant that this patient was never pregnant, although she had been married for three and a half years; that three years before she stopped menstruating for six months, and that she was suffering with hyperthyroidism. In 1913, Chvostek [27] emphasized the fact that the constitution of the patient plays a great rôle in the development of this disease.

CASE 3.—*Rudimentary gallbladder.*

A. L., a man, aged 22, a clerk, single, during the last ten months had had burning pain in the epigastrium which was relieved for one hour by food. The patient did not have cramps. On physical examination, the pulse rate was 96; the blood pressure was 128 systolic and 80 diastolic. A soft systolic murmur was heard over the base of the heart. Abdominal tenderness was not present. Both inguinal rings were large. The urine, stool and Ewald test meal were normal. The blood count was normal, except for an increase in the lymphocytes (46 per cent). The icteric index was 8.2. The blood Wassermann reaction was negative. Fluoroscopic and roentgenographic examination of the gastro-intestinal tract revealed a moderately ptosed stomach. The appendix remained filled forty-eight hours after a barium meal. At that time the rest of the large intestine was empty.

Twelve hours after the administration of the dye (tetraiodophenolphthalein sodium) by mouth, roentgenograms showed the gallbladder distinctly. It was about one-third the normal size and conical, and its fundus tapered to a point (fig. 5). Two hours after the ingestion of a fat meal, it was still about one-half full (fig. 6).

Endocrinologic and neurologic examinations (by Dr. William Leavitt) showed the following: The patient's height was 73.3 inches; the weight was

25. Bartel: Frankfurt. Ztschr. f. Path. **1-2**:206, 1916.

26. Bartel: Wien. klin. Wchnschr. **31**:605, 1918.

27. Chvostek: Ztschr. f. ang. Anat. **1**:27, 1913.

165 pounds (17.8 Kg.). The circumference of the head, which was large and brachycephalic, was 22 inches. The cephalic index was 87 +. His bones were long, and he was long-waisted. The skin was fair and fine. There was moderate growth of hair over the upper part of the chest, anteriorly and posteriorly. The pubic hair was of the male type of distribution. The face

Fig. 5 (case 3).—Cholecystogram of rudimentary gallbladder, conical in shape, with fundus tapering to a point.

was long; the nose was sharp, prominent and thin. The eyeballs were deeply set. The palate was high and arched and the teeth were regularly set. The neck was long, thin and strong, but not massive. He had cyanosis of the hands and feet, but they were warm and moist. The lower part of the abdomen was prominent, suggesting visceroptosis. The genital organs were normal.

The results of the neurologic examination were negative. The patient was shy, and had a hesitant personality. He was of normal intelligence but lacked aggressiveness. He was passive and docile, and found it difficult to make advances. It is significant that he had a lymphocyte count of 46 per cent. The impression was that the abnormal development was of the "thymic type."

Rudimentary gallbladders about the size of a goose quill are described by Cursham,[28] Wilks[29] and Roth.[30] These extreme cases,

Fig. 6 (case 3).—Two hours after the ingestion of a fat meal, the gallbladder is about one-half full.

however, are usually accompanied by obliteration of the bile ducts with subsequent development of jaundice and biliary cirrhosis, terminating in death in early infancy. The case under consideration answers fairly

28. Cursham: London Med. Gaz. **26**[2]:388, 1840.
29. Wilks: Tr. Path. Soc. London **13**:119, 1862.
30. Roth: Virchows Arch. f. path. Anat. **43**:296, 1868.

well to what Berg [31] calls "the gallbladder of rudimentary morphology." In this condition, the gallbladder is less differentiated from the cystic duct, more mobile, and its emptying power is impaired. Therefore, a disturbance is produced in the pressure regulation of the entire hepatic system, which may lead to deranged hepatic function. In this case the small size of the gallbladder, its conical shape, impaired power of concentration and delayed emptying time are the anatomic and physiologic evidences of abnormal structure and function. The high icteric index (8.2) suggests disturbed hepatic function. The age of the patient and the history of the case do not warrant the assumption that these deviations from the normal are due to pathologic changes in the gallbladder. On the contrary, his entire make-up, as evidenced by his somatic and mental characteristics, strongly suggests the presence of developmental disturbances which are also the probable causes of this abnormal gallbladder.

EMBRYOLOGY OF THE GALLBLADDER

Felix [32] and Hammar [33] thought that the liver and its ducts develop simultaneously from the protrusion at the ventral portion of the foregut, that the cranial portion of this protrusion forms the liver and its caudal portion, the ducts. This has been definitely disproved by Ludwig; [34] according to him, only the liver is formed by the protrusion. However, as it moves away from the foregut, it remains united to it by a strand which undergoes canalization and forms the primitive common bile duct. This is still lined with liver cells which subsequently become the glands of the ducts. The primitive gallbladder is formed by a depression in this duct; the permanent gallbladder arises by the formation of a bud in this depression. The cells in this bud proliferate and give rise to a number of cavities, each separated from its neighbors by septums. Eventually, they fuse and form one cavity. The primary gallbladder becomes the cystic duct. The permanent gallbladder is not lined by liver cells and therefore does not contain glands (Aschoff and Bacmeister [35]). When the cavities fail to fuse properly, various congenital anomalies may arise.

SUMMARY

1. Methods of precision used in the diagnosis of disease may become useful instruments of investigation in the hands of the clinician. This is illustrated by the contributions of roentgenology to the knowledge of

31. Berg: Arch. f. klin. Chir. **126**:327, 1923.
32. Felix: Arch. f. Anat. u. Physiol., 1892, p. 281.
33. Hammar: Arch. f. Anat. u. Physiol., 1893, p. 123.
34. Ludwig: Anat. Hefte. First Part **56**:513, 1918-1919.
35. Aschoff and Bacmeister: Die Cholelithiasis, Jena, Gustav Fischer, 1909, p. 17.

the anatomy and physiology of the stomach and its response to drugs. It is further illustrated by the valuable information gained in the physiology of the gallbladder since the introduction of cholecystography in clinical medicine.

2. Three anomalous gallbladders, most likely of congenital origin, are described. In the course of routine examinations, these were detected by means of cholecystography. The three types are:

(*a*) Hour-glass gallbladder. This case is most likely of congenital origin.

(*b*) Gallbladder resembling a "Phrygian cap." This is associated with hyperthyroidism, menstrual irregularity and sterility. It is therefore considered part of a general constitutional disturbance.

(*c*) Rudimentary gallbladder. This answers the description of Berg's "gallbladder of rudimentary morphology." The patient also conforms to that variety of abnormal development known as the "thymic type."

ELECTIVE LOCALIZATION OF STREPTOCOCCI ISOLATED FROM CASES OF PEPTIC ULCER *

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As yet there is no universal agreement concerning the pathogenesis of the peptic ulcer which occurs spontaneously in man. Voluminous articles have been devoted to the effort to establish some causative factors, but the various theories and experimental reports have generally led rather to divergence than to convergence of ideas as to the particular etiologic agent.

It is true that ulcerations in the gastric and duodenal mucosa have been produced in various ways, but these experimental methods are usually so foreign to what could actually occur clinically that they can have little practical bearing on the etiology of the ulcer in man.

REVIEW OF THE LITERATURE

Ulcers of the stomach have been produced experimentally by interfering with nerve supply,[1] by section of the spinal cord [2] and by section or stimulation of the vagus or the sympathetic nerves. Durante [3] and Vedova [4] by such methods produced fairly well formed ulcers in a considerable number of experiments. Similarly, lesions have been produced by injuring the mucosa mechanically, by excising pieces, by the use of sutures,[5] by the application of the actual cautery or silver nitrate and nitric acid,[6] by injecting into or beneath the mucosa such substances as

* From the Division of Experimental Bacteriology, The Mayo Foundation.

1. Stahnke, Ernst: Experimentelle Untersuchungen zur Frage der neurogenen Entstehung des Ulcus ventricule zugleich ein Beitrag zur pathologischen Physiologie der Mageninnervation, Arch. f. klin. Chir. **132**:1, 1924.

2. Kawamura, K.: Ueber die experimentelle Erzeugung von Mageneschwüren durch Nervenläsionen, Deutsche Ztschr. f. Chir. **109**:540, 1911.

3. Durante, Luigi: The Trophic Element in Origin of Gastric Ulcer, Surg. Gynec. Obst. **12**:399, 1916.

4. Vedova, R. D.: Richerche sperimentali sulla patogenesi dell' 'ulcera gastrica, Policlinico **6**:1153, 1899-1900.

5. Katzenstein, M.: Beitrag zur Entstehung des Magengeschwürs, Arch. f. klin. Chir. **101**:1, 1913.

6. Quincke, H., and Daettwyler: Untersuchungen über Magengeschwüre, Cor.-Bl. f. schweiz. Aerzte. **5**:101, 1875.

foreign protein in sensitized animals,[7] gastrotoxic serum,[8] silver nitrate [9] and alcohol; [10] by the injection of lead chromate [11] and fat [12] to produce embolic lesions; by intravenous injection of poisons such as pilocarpine, phenol, chloroform, bile salts,[13] B-tetra-hydronophthylamine,[14] epinephrine,[15] diphtheria toxin [16] and filtrates of various bacteria and by extirpation of the suprarenal and thyroid glands.[17] Some have maintained that ulcers may be due to a disproportion between the gastric pepsin and the antipepsin of the blood serum.[18] Mann and Williamson [19] produced single subacute and chronic ulcers in the jejunum of dogs in a high percentage of cases when anastomosis of the jejunum to the stomach was performed and when the duodenum with its alkaline content was drained into the terminal ileum. Ulcerations have been produced in many sites in the stomach by

7. Ivy, A. C., and Shapiro, P. F.: Experimental Production of Gastric Ulcer by Local Allergy, Preliminary Report, J. A. M. A. **85**:1131 (Oct. 10) 1925.

8. Bolton, Charles: Experimental Production of Gastric Ulceration by Injection of Gastrotoxin, Lancet **1**:1330, 1908.

9. Friedman, J. C., and Hamburger, W. W.: Experimental Chronic Gastric Ulcer, J. A. M. A. **63**:380 (Aug. 1) 1914.

10. Licini, Cesare: Ueber experimentelle Erzeugung von Mageneschwüren, Beitr. z. klin. Chir. **79**:462, 1912.

11. Cohnheim, J. F.: Lectures on General Pathology, London, New Sydenham Society **3**:879, 1890.

12. Schridde: Experimentell erzeugte Magengeschwüre bei Murschweinchen (Diskussion), Verhandl. d. deutsch. path. Gesellsch. **11**:234, 1907.

13. Sellards, A. W.: Ulceration of the Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of Bile Salts, Arch. Int. Med. **4**:502 (Nov.) 1909. Smith, G. M.: An Experimental Study of the Relation of Bile to Ulceration of the Mucous Membrane of the Stomach, J. M. Research **30**:147, 1914.

14. Elliott, T. R.: The Experimental Formation of Acute Gastric Ulcers, Quart. J. Med. **7**:119, 1914.

15. Friedman, G. A.: The Influence of Removal of Adrenals and One Sided Thyroidectomy upon the Gastric and Duodenal Mucosa, the Experimental Production of Lesions, Erosions, and Acute Ulcer, J. M. Research **32**:287, 1915; Probable Endocrine Origin of Peptic Ulcer, New York M. J. **107**:1205, 1918.

16. Rosenau, M. J., and Anderson, J. F.: A Stomach Lesion in Guinea Pigs Caused by Diphtheria Toxin and Its Bearing upon Experimental Gastric Ulcer, J. Infect. Dis. **4**:1, 1907.

17. Carlson, A. J., and Jacobson, Clara: Further Studies on the Nature of Parathyroid Tetany, Am. J. Physiol. **28**:133, 1911. Mann, F. C.: A Study of the Gastric Ulcers Following Removal of the Adrenals, J. Exper. Med. **23**:203, 1916. Also see footnote 15.

18. Einstein, Otto: Ueber die verdauungshemmende Wirkung von Antipepsin des Blutserums bei Magengesunden und Magengeschwürskranken, Med. Klin. **20**:1578, 1924. Leiblein, Viktor: Ueber den Antipepsingehalt des Blutes in Fällen von ulcus ventruculi, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:391, 1912.

19. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

roentgen rays.[20] In 1853, Virchow [21] initiated the idea, which has been accepted by many, that spasms or portal stasis might give rise to hemorrhagic infarction and subsequent ulceration. Various functional disturbances of the stomach, such as hypotonia and hypertonia, have supposedly produced lessened resistance by interfering with the nerve or blood supply, and thus have led to the formation of ulcer by subsequent digestion.[22] Hamburger [23] stated that abrasions resulting from traumatization by food or from emboli or bacteria produce acute ulceration which in the presence of hypersecretion and hyperacidity from some underlying cause, such as vagotonia or reflex pylorospasm, may produce chronic ulcers. Morris [24] stated that the ulcer probably starts with a proliferating endarteritis due to some toxic excretion and suggests *Bacillus coli* as the possible toxic agent. Wilkie,[25] from postmortem study, concludes that toxic absorption from the appendix or colon could produce an irritable condition of the autonomic nervous system with tendency to ulcer formation. The relation of infection to the formation of ulcer has been demonstrated by many clinical and experimental investigations. It has infrequently been noticed that ulcers of the stomach occur during severe and fatal infections, particularly those of streptococcic origin. Intravenous injection of pus by Leber [26] and Cohn [27] and of streptococci and staphylococci by Letulle [28] produced similar lesions, as did also the pneumococci injected by Bezancon and Giffon.[29] Boettcher [30] in 1874 demonstrated bacteria in the edges and floor of ulcers, and Dudgeon and

20. Wolfer, J. A.: Chronic Experimental Ulcer of the Stomach, Its Clinical Significance, J. A. M. A. **87**:725 (Sept. 4) 1926.

21. Virchow, Rudolph: Historisches, Kritisches und Positives zur Lehr der Unterleibs Affektionen, Arch. f. path. Anat. u. Physiol. **5**:281, 1853.

22. Möller, S.: Die Pathogense des Ulcus ventriculi mit besonderer Berücksichtigung der neueren experimentellen Ergebnisse, Ergebn. d. inn. Med. u. Kinderh. **7**:520, 1911.

23. Hamburger, W. W.: Discussion on Experimental Studies in the Production of Chronic Gastric Ulcer, M. Rec. **86**:898, 1914.

24. Morris, R. T.: The Etiology of Gastric Ulcer, M. Rec. **84**:854, 1913.

25. Wilkie, D. P. D.: Observations on the Pathology and Etiology of Duodenal Ulcer, Edinburgh M. J. **13**:196, 1914.

26. Lebert, quoted by Rosenow, E. C.: The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333, 1916.

27. Cohn, B.: Klinik der embolischen Gefässkrankheiten, mit besonderer Rücksicht auf die arztliche Praxis, Berlin, Hirschwald, 1860, vol. 16, p. 696.

28. Letulle, M.: Origine infectieuse de certains ulcères, simples de l'estomac ou du duodenum, Bull. et mém. Soc. méd. d. hôp. de Paris **5**:360, 1888.

29. Benzancon, F., and Giffon, V.: Ulcérations gastriques au cours de la septicémie pneumococcique chez le cokaye, Bull. et mém. Soc. anat. de Paris **1**: 409, 1899.

30. Boettcher, H.: Zur Genese des perforirenden Magengeschwürs, Dorpat. med. Ztschr. **5**:148, 1874.

Sargent [31] isolated a diplostreptococcus from the edges of ulcers and peritoneal exudate in four cases of ulcer after death from perforation. Steinharter [32] reported his work on the production of gastric ulcers and duodenal hemorrhagic lesions by the injection of clumped colon bacilli; Türck [33] claimed to have found typical round ulcers of the stomach and duodenum in dogs after they had been fed colon bacilli for a long period. Hoffman [34] isolated an aerobic nonmotile bacillus from the tonsils and gastric contents in a few patients who had ulcers and claimed to have produced ulcers in animals with the organism and its filtrate.

Whether a focus of infection, usually symptomless, and apparently harmless in itself, can under certain conditions act as a distributing center for micro-organisms which have acquired particular evasive and localizing power, and produce in distant places acute, subacute or chronic inflammatory lesions, is an interesting as well as a much discussed problem. As long ago as 1801, Benjamin Rush [35] noted a relationship between infected teeth and systemic disease. However, little attention was paid to it until Billings,[36] Rosenow,[37] and their co-workers made extensive clinical and experimental investigations of this question. Rosenow, in 1913, reported experiments in which it was found that the intravenous injection of streptococci of proper grade of virulence may be followed by ulcer of the stomach and duodenum; this ulceration is due to localized infection and secondary digestion. On the basis of these experiments, the theory that the usual form of gastroduodenal ulcer may be due to a localized infection by streptococci having elective affinity for the mucous membrane of the stomach and duodenum took definite form. In a series of subsequent studies, much evidence

31. Dudgeon, L. S., and Sargent, P. W.: The Erasmus Wilson Lectures on Peritonitis: A Bacteriological Study, Lancet **1**:473, 1905.

32. Steinharter, E. C.: A Preliminary Note on the Experimental Production of Gastric Ulcers by Intravenous Injection of Clumped Colon Bacilli, Boston M. & S. J. **169**:81, 1913.

33. Türck, F. B.: Further Observations on the Etiology and Pathology of Peptic Ulcer, Brit. M. J. **1**:922, 1907.

34. Hoffman, Albert: Experimental Gastric and Duodenal Inflammation and Ulcer Produced with Specific Organism Fulfilling Koch's Postulates, Am. J. M. Sc. **170**:212, 1925.

35. Rush, Benjamin, quoted by Duke, W. W.: Oral Sepsis in Its Relation to Systemic Disease, St. Louis, C. V. Mosby Company, 1918, p. 124.

36. Billings, Frank: Chronic Infectious Endocarditis, Arch. Int. Med. **4**:409 (Nov.) 1909.

37. Rosenow, E. C.: The Production of Ulcer of the Stomach by the Injection of Streptococci, J. A. M. A. **61**:1947 (Nov. 29) 1913; The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333, 1916; Specificity of Streptococcus of Gastroduodenal Ulcer and Certain Factors Determining Its Localization, J. Infect. Dis. **33**:248, 1923; Studies on Elective Localization: Focal Infection with Special Reference to Oral Sepsis, J. Dent. Res. **1**:205, 1919.

in support of this theory has been reported. In 1914, Rosenow and Sanford reported the observation of diplococci in the tissues in a series of chronic ulcers excised at operation. Rosenow, in 1915, reported the isolation of streptococci (from excised ulcers and from foci of infection in patients suffering from peptic ulcer) which had elective affinity for the stomach and duodenum when injected intravenously into animals and which produced hemorrhage and ulceration in a high percentage of these animals. He also showed that this did not occur with streptococci obtained from the metastatic lesions and from foci of infection in patients free from ulcer. In a further experimental study with streptococci from ulcer, reported in 1916, he showed that the ulcers produced by the injection of streptococci resembled the ulcers of man in situation, in gross and microscopic appearance and in their tendency to perforate and to persist along the lesser curvature, in the pylorus and in the first part of the duodenum. The streptococcus was frequently demonstrated microscopically in the hemorrhagic and ulcerated areas, not only in the lesions of the stomach and duodenum of animals injected intravenously with the ulcer-producing streptococcus but also in the chronic jejunal ulcers of dogs. Rosenow also isolated a similar streptococcus from spontaneous ulcers of the stomach of the dog, calf, cow, sheep and swine, which had elective affinity for the stomach of animals when injected intravenously. It is also of significance that in five of seven chronic jejunal ulcers in dogs produced by the duodenal drainage method of Mann and Williamson, he also was able to isolate a streptococcus with similar selective action.

In 1923, he again published further corroborative data showing that the ulcer-forming streptococcus produces a poison within itself and also a free poison in broth cultures which, when injected, injures selectively the gastric and duodenal mucosa and produces hemorrhage, leukocytic infiltration and ulceration. By immunizing one group of rabbits to ulcer strains and another group to encephalitis strains of streptococci, and then injecting all the rabbits with vulnerable doses of living ulcer-forming streptococci, he found that ulcers did not form in the animals immunized to the ulcer strains whereas they did appear in the control rabbits immunized to encephalitis strains. He also found that rabbits immunized to ulcer-producing streptococci obtained from the ulcers in dogs were immune to the ulcer-producing streptococci obtained from ulcers in man.

Meisser,[38] working with the streptococcus from oral foci of infection, was able to show that in animals injected intravenously with these organisms lesions usually developed which were similar to those of the patient,

38. Meisser, J. G.: Further Studies on Elective Localization of Bacteria from Infected Teeth, J. Am. Dent. Assn. **12**:554, 1925.

while the injection of equally large doses of streptococci from the saliva or mucosa of the mouth in most instances failed to produce any specific lesions. He also produced chronic foci of infection in dogs by devitalizing and infecting their four cuspids with streptococci isolated from the infected teeth of patients suffering from ulcer of the stomach. In 65 per cent of these dogs hemorrhages or ulceration or both were produced. Section of some of these areas showed definite scarring and other evidences of chronicity. Of thirty-four dogs in which Rosenow and Meisser infected the teeth in exactly the same manner with strains of streptococci from nine patients suffering from nephrolithiasis, thirty developed lesions in the genito-urinary tract. In none were any gastro-duodenal lesions produced.

Haden [39] reported a series of twelve cases of peptic ulcer in which he made a study of foci of infection in dental areas, and he obtained localization in the stomach and duodenum in 53 per cent of forty-five rabbits injected. For control, 535 rabbits were injected intravenously with cultures from dental foci of patients not known to be suffering from peptic ulcer; similar lesions were manifested in only 7 per cent of the rabbits given these injections.

Nakamura,[40] studying elective localization in cases of ulcer of the stomach in Rosenow's laboratory, found gross evidence of infection of the tonsils in nine selected cases of gastric or duodenal ulcer. In forty-six (70 per cent) of the rabbits injected with the strains isolated from the tonsils of the nine patients, hemorrhages or ulceration or both were found in the mucous membrane of the stomach or duodenum, in contrast to lesions of the joints in 30 per cent, of the muscles in 2 per cent, of the heart in 6 per cent and of the kidneys in 4.5 per cent.

Frick [41] stated that according to his clinical experience there seems to be no doubt that Rosenow's theory of the elective affinity of a specific streptococcus, of a certain grade of virulence, for the gastric or duodenal mucosa is correct and that a specific streptococcus is the common cause of peptic ulcer.

In the wall of a duodenal ulcer which was the source of hemorrhage in an infant dying with melena neonatorum, Kennedy [42] demonstrated gram-positive streptococci, morphologically like those found in ulcers in men.

39. Haden, R. L.: The Elective Localization of Bacteria in Peptic Ulcer, Arch. Int. Med. **35**:457 (April) 1925. Haden and Bohan, P. T.: Focal Infection in Peptic Ulcer, J. A. M. A. **84**:409 (Feb. 7) 1925.

40. Nakamura, T.: A Study of Focal Infection and Elective Localization in Ulcer of the Stomach and in Arthritis, Ann. Surg. **79**:29, 1924.

41. Frick, Anders: Medical Treatment of Peptic Ulcer Without Alkali, J. A. M. A. **82**:595 (Feb. 23) 1924.

42. Kennedy, R. L. J.: Etiology and Healing Process of Duodenal Ulcer in Melena Neonatorum, Am. J. Dis. Child. **31**:631 (May) 1926.

Smithies [43] stated that 33 per cent of his 522 proved cases of gastric ulcer were infectious in origin. White [44] and Stewart [45] stated that as a result of all evidence presented, they believed that infection and intoxication are the most important direct causes of acute ulcer. Eusterman [46] summarized the clinical evidence for the infectious origin of peptic ulcer in the light of recent experimental work and expressed the opinion that in certain types of ulcer it is the only tenable theory at this stage of medical progress.

Certain recent observations of foreign investigators on the resected ulcer of man corroborate the work done in this country. Konjetzney [47] found a high percentage of gastritis or duodenitis about these resected ulcers, and Kalima found evidence of gastritis in all resected specimens of ulcer. Puhl [48] showed that all cases of peptic ulcer are accompanied by gastritis or duodenitis of more or less severity, most marked in the region of the pyloric glands. In his series of 140 resected gastric and duodenal ulcers, he found numerous small erosions even far distal to the chronic ulcer, superimposed on an inflammatory process. There were all gradations from the acute hemorrhagic erosion to the chronic ulceration. He was therefore inclined to believe that the same factors which initiated one initiated the other. He was able to demonstrate bacteria in the sections, chiefly gram-positive diplococci, but was unable to culture any of them, and therefore did not draw any definite conclusions concerning them.

In a recent paper, Moutier [49] said that he had been able to demonstrate the diplostreptococcus deep in the inflammatory zone surrounding the ulcer. He said that since the organisms are most numerous adjacent to the muscularis, they cannot be the result of contamination, and that therefore certain peptic ulcers at least are infectious in origin.

The mass of accumulated data, both clinical and experimental, shows that the probable cause of ulcer is still a subject of much debate among clinicians. It is universally agreed that the fundamental change per se in the gastric or duodenal mucosa is imparied nutrition in a localized

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43. Smithies, Frank: Significance of Etiologic Factors in the Treatment of Peptic Ulcer, J. A. M. A. **74**:1555 (June 5) 1920.

44. White, F. W.: The Etiology and Pathology of Perforating Gastric and Duodenal Ulcer, Boston M. & S. J. **177**:555, 1917.

45. Stewart, M. J.: The Pathology of Gastric Ulcer, Brit. M. J. **2**:955, 1923.

46. Eusterman, G. B.: Clinical Notes on Recurrent Ulcer of the Stomach and Duodenum; Incidence, Diagnosis and Etiology, Minnesota Med. **6**:698, 1923.

47. Konjetzney, G. E.: Die chronische Gastritis des Ulcusmagens, Zentralbl. f. Chir. **1**:1026, 1923.

48. Puhl, Hugo: Ueber die Bedeutung entzündlicher Prosesse für die Entstehung des Ulcus ventriculi et duodeni, Arch. f. path. Anat. u. Physiol. **260**:1, 1926.

49. Moutier, F.: Étude anatomo pathologique: Les étapes infectieuses de l'ulcère, Arch. d. mal. de l'app. digestif **16**:18, 1926.

area with subsequent necrosis, sloughing and digestion in the injured area by the corrosive action of the acid gastric juice. The mechanical, corrosive, thrombotic, embolic and neurogenic factors are emphasized by the exponents of the different theories. The theory of infection, however, has gained more prominence in recent years chiefly as a result of the work of Rosenow and his co-workers; yet all gastro-enterologists do not grant that the chief cause of ulcer is a specific streptococcus, although the vast majority consider the focus of infection as at least partly responsible.

One of the best proofs of a causal relationship of bacteria to systemic disease is the reproduction of the patient's lesion in animals by the injection of the organisms isolated from the lesion or the septic foci of the patient. Ability to reproduce the lesions in this way not only clarifies the etiology, but demonstrates the specificity of certain organisms for a particular type of tissue which Rosenow has so aptly termed "elective localization."

EXPERIMENTAL INVESTIGATION

The present investigation was undertaken to prove or disprove certain impressions gained in a study of peptic ulcer which seemed to have an important bearing on the etiology of clinical peptic ulcer. As the work of Rosenow and of others who have followed his technic has shown conclusively that a specific streptococcus is harbored by the patient suffering from ulcer, and that when isolated and inoculated into animals this organism will produce lesions similar to those in man, and since in many cases of primary or recurring ulcer there is rather marked evidence of focal infection, two groups of cases of ulcer were studied. In one group, a series of consecutive cases extending over a period of six months was studied to determine whether streptococci were being harbored in every case; this was done so far as such investigation was permitted and desirable clinically. The next step was to determine whether acute and subacute lesions could be reproduced in animals by intravenous injection, and chronic lesions by inoculating the organisms into the devitalized teeth of dogs. In the second series of eleven cases of peptic ulcer resected at operation, the resected ulcers as well as the suspected foci were carefully investigated for ulcer-producing streptococci.

Technic.—The method of obtaining the culture varied with the focus. If the focus was the tonsil, a culture was obtained by using a small laryngeal mirror with the mirror so bent as to be almost in a straight line with the handle. The tongue was depressed with an illuminated tongue depressor and the sterilized laryngeal mirror was then inserted between the tonsil and the anterior pillar, and pressure applied backward and mesially toward the base of the tonsil. This procedure caused necrotic and puslike material to ooze from the depths of the crypts; the material was then scooped up with the laryngeal mirror and transferred with

a sterile swab from the mirror to a tube containing 2 cc. of gelatin-Locke solution, from which cultures were made in various mediums.

If the focus was a tooth, the operative field was wiped off with sterile gauze, painted with 2 per cent iodine followed by alcohol, and then dried with sterile gauze. The tooth was then extracted with sterile forceps, and while still held in the forceps, its apical one-fourth was nipped off with sterile nippers into small tubes containing Locke's solution and white sand, according to Haden's method. This was shaken for ten or fifteen minutes and then inoculated into the various culture mediums.

If the focus was the prostate, the glans was washed with soap and water followed by a sterile solution of physiologic sodium chloride. Then the posterior and anterior urethra were copiously irrigated with a similar sterile solution. The prostate was then massaged and the expressed material caught directly in tubes containing gelatin-Locke solution for culture. If the cervix was the suspected focus, a sterile speculum was used; a sterile swab was used to wipe off the external part and to secure superficial micro-organisms, while a second one was inserted into the canal or any eroded places for a culture.

The surgically resected peptic ulcers were cultured immediately after being excised. A portion of the ulcer was thoroughly shaken in three changes of sterile solution of sodium chloride to remove as much superficial contamination as possible, then emulsified in a sterile manner in a mortar with white sand and 4 cc. of sodium chloride solution; cultures were then made from this emulsion. All of the cultures were plated aerobically on blood-agar plates, and inoculated into glucose-brain agar and glucose-brain broth with and without a top layer of petrolatum (not liquid petrolatum) made according to Rosenow's method.

The blood-agar plate served as a control, especially in cultures from teeth, because the large majority of the strains which produced lesions in rabbits, when in the primary culture, grew poorly or not at all on blood-agar plates. The tall tubes of glucose-brain agar kept the colonies separated and were therefore a good index of the degree of infection present. The glucose-brain broth furnished the correct oxygen tension for growth, and such cultures were used for animal experiments. In all of the experiments, the rabbits were taken from a common stock used also by investigators in other fields of research without special regard to pedigree as long as they were healthy. Freshly isolated cultures, approximately from eighteen to twenty-four hours old, were inoculated intravenously into the marginal vein of the ear in dosages varying from 2 to 12 cc., depending on the size of the rabbit and the density of the culture. This injection was repeated once or twice with rapidly made subcultures, depending on the condition of the rabbit or the particular purpose of the experiment. For example, repeated injections were given when we wished to produce lesions in various stages of healing. The size of the doses also varied because the production of lesions in animals by injection of streptococci is not a stereotyped and constant occurrence as is the ability of the bacillus of tuberculosis to infect guinea-pigs; the localizing power of strains varies in the rabbits just as it produces inconstant effects in man. Hence the dosage was varied in order that somewhere in that range we might produce all conditions suitable and reproduce in the animal the lesion of the patient. The average length of life of the rabbit was five or six days. The majority of the rabbits were chloroformed. Necropsy was performed as soon as possible after death because of the rapid postmortem changes which occur in the stomach. None of the dogs was chloroformed, but all were allowed to live indefinitely; they were examined as soon as possible after death.

RESULTS

Of the eighty consecutive cases studied, only one failed to reveal a focus at the time of admission. This was a case of primary duodenal ulcer. Septic tonsils and two infected teeth had been removed a few weeks prior to registration because of choroid retinitis. In all of the remaining seventy-nine cases, eighteen of recurring and sixty-one of primary ulcer, one or more foci of infection were found in teeth, tonsils or prostate. The green-producing streptococcus was isolated either in pure or in mixed culture, and when injected intravenously into rabbits, produced hemorrhages, erosions or ulcerations in either the stomach or the duodenum or in both. In the three women in our first series, all the cultures from the cervix were negative or of no consequence.

The prostate was found to be the only apparent focus of infection in ten cases and one of several foci in thirty-one of the seventy-six cases in men. In twenty-three of these the infection in the prostate was clinically graded 1 or 2, while in one case in which the prostate was normal clinically, a culture yielded a pure growth, a green-producing streptococci which produced lesions when injected into animals. The tonsils or tonsillar tags furnished the only recognizable focus in twenty-nine cases, and in only eleven of these were the tonsils considered septic clinically. The teeth served as the only demonstrable focus in twelve cases. The majority of the teeth from which cultures were taken were devitalized but roentgenologically negative. They were found to be infected, however, as often as were the devitalized, roentgenologically-positive teeth, and cultures from their apexes often produced more typical lesions of the stomach and duodenum of rabbits than did the cultures of the devitalized, roentgenologically-positive teeth.

One hundred and three strains of green-producing streptococci were obtained from various foci of the 61 cases of primary ulcer; these were injected into 219 rabbits (table 1). Lesions of the stomach or duodenum were obtained in 137 (63 per cent) of the animals injected. In contrast to this, lesions were produced in the gallbladder in only 1 per cent, in the appendix in 8 per cent, in joints in 3 per cent, in the kidneys in 3 per cent and in the heart in 1 per cent. Of the 103 strains of streptococci, 27 were recovered from dental areas of infection; 65 animals were injected with the strains, and lesions of the stomach and duodenum were found in 39 (60 per cent). Forty-nine strains were obtained from tonsils or tonsillar tags; 106 animals were injected with these strains, and similar lesions were found in 76 (72 per cent). Twenty-seven strains recovered from the prostate were injected into 48 animals, and similar lesions were found in 25 (52 per cent). Of the 34 strains obtained from 18 cases of recurring ulcer, 7 were from dental areas of infection; 21 animals were injected with these 7 strains, and

lesions in the stomach or duodenum were obtained in 17 (81 per cent). Fifteen strains were obtained from tonsillar foci and injected into 36 animals; lesions occurred in the stomach or duodenum in 26 (72 per cent). Twelve strains were obtained from the prostate and injected into 19 animals, in 11 of which (58 per cent) lesions were found in the stomach or duodenum. Altogether 34 strains of green-producing streptococci were obtained from cases of recurring peptic ulcer; these were injected into 76 animals, and of these 54 (71 per cent) manifested gastric or duodenal lesions. In only 2 per cent were there lesions in the gallbladder, in 4 per cent in the appendix, in 4 per cent in the joints, in 5 per cent in the kidney and in 1 per cent in the heart (table 1).

In contrast to these are the control rabbits (table 1) previously reported on by one of us,[50] which were injected with cultures from foci

TABLE 1.—*Experimental Peptic Ulcer*

Source of Culture	Number of: Strains Cultured	Strains Positive	Rabbits Injected	Primary Ulcer: Percentage of Rabbits Having Lesions of the: Stomach or duodenum	Gallbladder	Appendix	Heart	Kidneys	Joints
Teeth.....	27	21	65	60	..	5	..	2	5
Tonsils.....	49	38	106	72	2	2	..	3	..
Prostate.....	27	21	48	52	..	10	2	2	2
Total.....	103	80	219	63	1	8	1	3	3
Recurring Ulcer									
Teeth.....	7	7	21	81	10	..	..	5	10
Tonsils.....	15	13	36	72	..	6	3	8	3
Prostate.....	12	10	19	58	..	5	..	..	..
Total.....	34	30	76	71	2	4	1	5	4
Controls (undiagnosed)	77	..	190	3	2	..	3	2	7

in cases in which no definite diagnosis was made. In this group there were lesions of the stomach and duodenum in only 3 per cent of the animals injected, of the heart in 3 per cent, of the joints in 7 per cent and of the gallbladder and kidneys in 2 per cent. It is readily seen that there is no marked selectivity of the micro-organisms in the control group for any part of the body, while the strains isolated in cases of peptic ulcer show definite selectivity for the stomach and duodenum.

The localizing power of the streptococcus so constantly found in the infective foci in cases of peptic ulcer is further illustrated by the results obtained from another series of 11 cases of peptic ulcer in which operation was performed. At operation, gastric ulcer was found in 4 of the 11, duodenal ulcer in 4 and gastrojejunal ulcer in 3. In 10 of these 11 cases, the green-producing streptococcus was isolated from the

50. Nickel, A. C.: The Localization in Animals of Bacteria Isolated from Foci of Infection, J. A. M. A. **87**:1117 (Oct. 2) 1926.

resected ulcers, and all 10 strains produced specific lesions in rabbits. In 28 of 31 rabbits injected intravenously with these strains, hemorrhagic erosions or ulcers were found in the stomach or duodenum (table 2). The infective foci in these 11 cases were investigated in the same manner as in our first series. A tonsillar or nasopharyngeal culture was obtained in every case, and in 9 of the 11 injections into experimental animals it produced gastric or duodenal lesions. Of the 22 rabbits injected intravenously with these tonsillar and nasopharyngeal cultures, lesions of the stomach or duodenum were found in 13. Two of 3 cultures obtained from the teeth in these cases produced gastric or duodenal lesions in rabbits, and similar lesions were found in 3 of the 8 rabbits injected with the cultures from the teeth. Similarly, 1 of 6 cultures from the prostate in this series contained streptococci, and a rabbit injected with this cul-

TABLE 2.—*Incidence of Lesions in Rabbits Injected with Streptococci Isolated from Operative Cases of Peptic Ulcer*

Source of Streptococci	Number of Strains		Number of Animals		Lesions in								
					Stomach		Duodenum,						
	Injected	Producing Specific Lesions	Injected	Showing Specific Lesions	Hemorrhage	Ulceration	Hemorrhage	Gallbladder	Appendix	Intestine	Heart	Lungs	Kidneys
Resected peptic ulcers in man..	10	10	31	28	19	14	6	..	..	1	..	..	2
Tonsils or nasopharynx	11	9	22	13	10	4	4	2	..	2	1	2	2
Teeth....	3	2	8	3	1	1	1	..	..	..	1	..	..
Prostate	1	1	1	1	1	..	..	..	..	..	..	..	..
Total.....			62	45	31	19	11	2	..	3	2	2	4
Percentage localization.....				73	..	..	..	3	..	5	3	3	7

ture likewise manifested peptic lesions. Thus, of 61 animals injected with cultures from peptic ulcers and infective foci in the cases of this second series, lesions of the stomach or duodenum were found in 45 (73 per cent), in contrast to lesions of the gallbladder, heart and lungs in 3 per cent, of the intestines in 5 per cent and of the kidneys in 7 per cent.

To determine still further the elective localizing power of these organisms, strains freshly isolated from rabbits with definite lesions of the stomach or duodenum were introduced into the pulp chambers of dogs' teeth in the hope of stimulating a chronic dental focus in man. In some of the dogs only the pulps of four teeth were infected; in others gastro-enterostomy also was performed. In both groups of dogs, those that lived only several months manifested submucous hemorrhagic lesions about the gastro-enteric stoma and distal loop of bowel, while in those that lived a year or longer definite chronic

ulcerations tended to form on the lesser curvature of the stomach or in the distal loop of the bowel; in several, perforation occurred. At necropsy a roentgenogram of the infected teeth frequently showed rarefaction at the apex, and the majority of the cultures obtained from the pulp chambers, as long as one and two-thirds years after inoculation, contained the living streptococcus which still maintained its ability to localize electively in the stomach and duodenum of rabbits when injected intravenously.

ILLUSTRATIVE CASES OF PEPTIC ULCER

CASE 1.—A Russian Jew, aged 39, entered the Mayo Clinic in June, 1923, with a history of "stomach trouble" for the previous nine years. This distress began

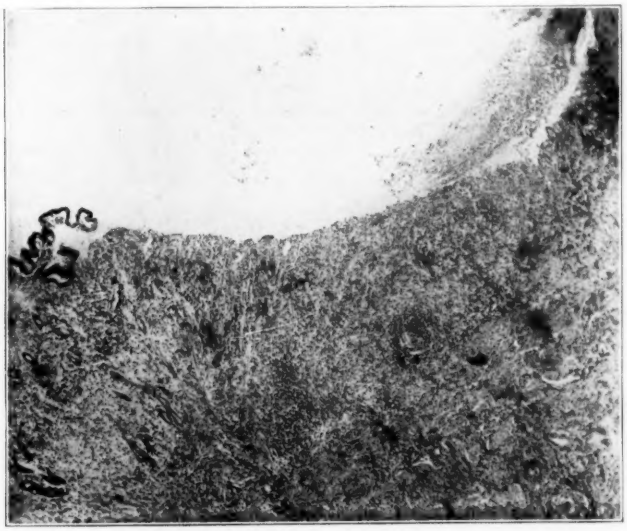

Fig. 1 (case 1).—Section through the side wall of a resected gastric ulcer of man showing marked cellular infiltration and necrotic material near the base. Hematoxylin and eosin stain; × 25.

as a dull pain in the epigastrium, at times accompanied by vomiting, and he often complained of flatulency. Definite symptoms of ulcer could not be elicited from the history. In January, 1915, appendectomy gave no relief. Three months later, gastro-enterostomy was performed and five months later, a second gastric operation (nature unknown). The patient was somewhat relieved for two months; he then went on a general diet and soon after began to complain of rather severe pain in the left side of the epigastrium; this pain was relieved by food. However, he suffered from continuous "full-pressure" pain in the same region. He followed the Sippy diet for three years, but was not greatly relieved. He did not vomit and did not have a hemorrhage.

The patient's physical condition was poor. The Wassermann test of the blood was negative. The total gastric acidity was 56 and free hydrochloric acid 42; a roentgenogram of the stomach was normal. Pyorrhea was present (graded 2), and there were four infected roots of teeth. Because of the persistence of the complaints and the presence of an indefinite mass to the left of the navel, an exploratory operation was performed on June 23. The stomach was adherent to the anterior abdominal wall at the site of a previous anastomosis, and at this site there was a perforating ulcer with a crater 1 cm. in diameter. The ulcer was excised and the anterior gastro-enteric anastomosis reconstructed. The patient improved after this operation, gained weight and had no gastric complaints for about one year. Because of trouble with the teeth and sore gums, all of the teeth and supposedly the root tips were extracted in August, 1924. The patient had failed, his mouth was sore, and he had lost 10 pounds (4.5 Kg.) in weight, which were never regained. He returned to the Mayo Clinic in January, 1926. Ten or eleven months prior to this, the old epigastric pain recurred and was constant except when temporarily relieved by food and alkali; at times it was severe, even when he was on a soft diet. There was a distinct mass to the left of the umbili-

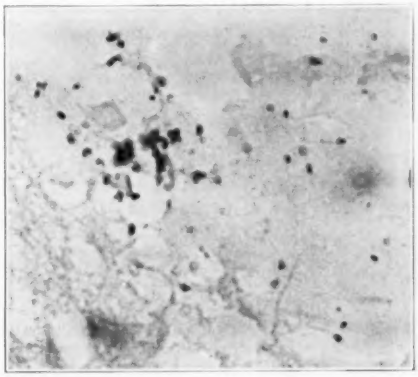

Fig. 2.—Many diplococci found in the depths of the wall of the ulcer, shown in figure 1. Gram-Weigert stain; × 1000.

cus, which was tender. The tonsils were medium-sized and contained soft plugs; the prostate was normal clinically and negative culturally, but there were five remaining tooth root tips. The roentgenogram of the stomach revealed a gastrojejunal ulcer. At operation it was found that the ulcer had recurred in the anterior portion of the stoma and was attached to the anterior abdominal wall in the scar tissue. The ulcer was 4 cm. in diameter and 2 cm. deep. The anatomosis was separated, the crater in the abdominal wall excised, the jejunum closed and the pyloric two thirds of the stomach resected. Section of the ulcer stained by the Gram stain revealed the diplococcus deep in the inflammatory tissues. The root tips were removed. In two of the four animals injected with the cultures, duodenal lesions were found. Cultures of the tonsils consisted of almost pure green-producing streptococci. The three rabbits injected with the culture from the tonsils manifested gastric or duodenal lesions.

The patient was free from symptoms on dismissal from the clinic. One year later, he returned for reexamination. He said that he had not any gastric distress.

CASE 2.—A man, aged 31, said that he had had periodic gastric distress since 1918, which he described as a gnawing pain two or three hours after meals, accompanied at times by tarry stools and flatulency and vomiting when he had eaten a heavy meal. Two courses of medical treatment in the hospital relieved the symptoms for a few months. For two months prior to coming to the Mayo Clinic, he had suffered from gastric distress and vomiting daily.

On examination, considerable tenderness was found in the midepigastrium. The systolic blood pressure was 120 and the diastolic 85. Total gastric acidity was 40 and free hydrochloric acid 20. A roentgenogram of the stomach revealed a perforating ulcer on the lesser curvature. At operation, two large perforating gastric ulcers were found near the lesser curvature, with considerable inflammatory reaction (fig. 1). Partial gastric resection, Billroth II, and appendectomy were performed.

In cultures made from emulsions of a portion of the resected ulcer there were green-producing streptococci; streptococci were also found in sections of the resected ulcer (fig. 2). All of the rabbits injected with this primary culture

Fig. 3.—Diffuse submucous hemorrhages in the first portion of the duodenum of a rabbit injected several times with a freshly isolated culture from the tonsil of a patient having peptic ulcer. Note also the hemorrhagic ulceration of the fundus; × 1.

manifested gastroduodenal lesions. Similar lesions were found in rabbits after they had been injected with cultures (from the patient's ulcer) passed once and twice through animals. In cultures from the patient's tonsils green-producing streptococci were found, which also produced hemorrhagic erosions when injected into two animals.

PATHOLOGIC OBSERVATIONS

The predominating causative organism in all of these experiments was found to be a green-producing streptococcus. Morphologically and according to sugar reactions, it was often indistinguishable from other green-producing strains of streptococci which were isolated in cases of arthritis, myositis and other conditions. However, when injected intravenously into rabbits and when inoculated into the teeth of dogs, it had

a marked tendency to localize in the stomach and duodenum instead of in the muscles, nerves or joints. In primary culture it grew poorly or not at all on a blood-agar plate, but it grew readily in partial-tension mediums, such as Rosenow's glucose-brain broth. The lesions produced by the streptococci were chiefly in the duodenum or pyloric portion of

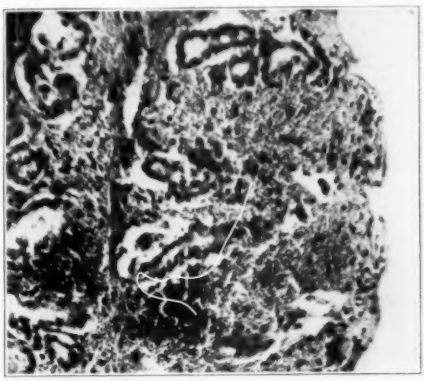

Fig. 4.—Blood-distended villi, with loss of glandular structure, of the hemorrhagic portion of the duodenum shown in figure 3. Hematoxylin and eosin stain; × 120.

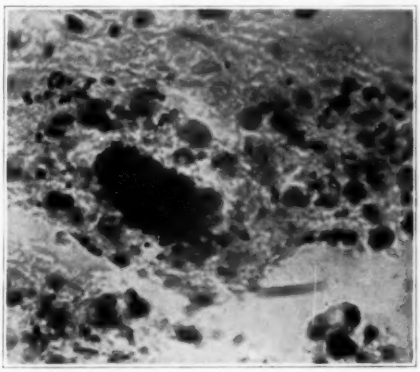

Fig. 5.—Diplococci scattered through all layers of the duodenum and practically occluding some of the smaller blood vessels beneath the hemorrhages of the duodenum shown in figure 3. Gram-Weigert stain; × 1000.

the stomach and sometimes in the fundus. When in the fundus they tended to heal rapidly, while in the pylorus and duodenum, the healing was slower; in this respect, the ulcers resembled those found in man. In rabbits which had received repeated injections, necropsy often

revealed lesions in various stages of healing, which seemed to indicate a relationship between the lesions and the injected material (fig. 3). The lesions of the stomach and duodenum both in rabbits and in dogs resembled those induced by Rosenow and Meisser. They consisted of submucous petechial hemorrhages, definite erosions with a hemorrhagic center and well-formed ulcers, often associated with free blood in the lumen. The petechial hemorrhages were generally superficial and multiple, and were widely disseminated in the stomach; but when they occurred in the duodenum, they were almost always confined to its first portion between the pylorus and ampulla. In advanced conditions, the hemorrhagic areas were often confluent and the glandular structure could hardly be differentiated (figs. 3 and 4). These hemorrhages were sometimes beneath the muscularis but more often nearer the surface of

Fig. 6.—A solitary duodenal ulcer on the posterior wall of the duodenum of a rabbit injected with a tonsillar culture on three successive days. The rabbit was chloroformed on the fourth day; × 1.

the mucosa; frequently the villi were so distended with blood and fluid that the content of the villus ruptured through the mucosa into the lumen of the stomach or duodenum. The amount of cellular infiltration varied but was never extensive. The bacteria were usually numerous, and sometimes were clumped inside the vessel wall almost occluding the lumen (fig. 5). In other instances, many such hemorrhagic areas were found, some of which had sloughed away, leaving definite erosions or ulcers with a base which sometimes consisted of submucosa or even of muscle, and which was covered with varying amounts of necrotic material (figs. 6 and 7). In these cases there was edema throughout the tissues. The nuclei of the surrounding cells were indistinct and stained poorly, and there was definite round-cell infiltration which often

extended down into the muscularis. Streptococci were often found mixed with equal numbers of other micro-organisms in the superficial necrotic layers. However, in the depths of the mucosa and submucosa and beneath the necrotic material, these other micro-organisms were not visible; here the streptococci were usually found in pairs near the smaller blood vessels (fig. 8), frequently beneath the muscularis and, in perforating cases, near the serosa.

COMMENT

Our results agree favorably with those reported previously by Rosenow and his co-workers and those of Haden and Bohan. If the

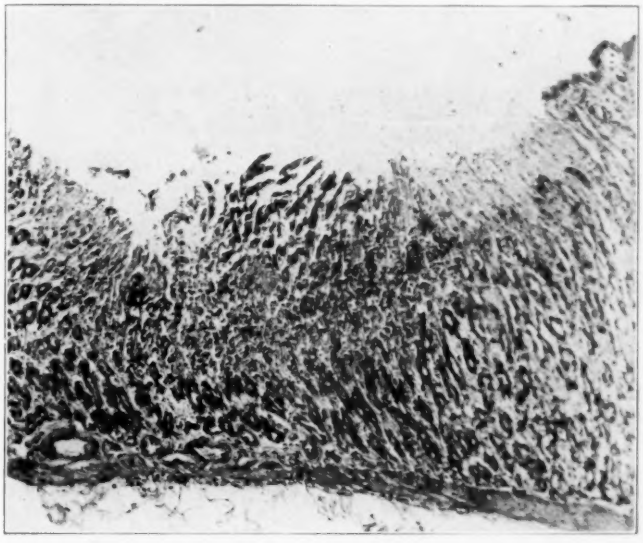

Fig. 7.—Section through an ulcer of the duodenum of a rabbit. Note the marked necrosis with loss of tissue, scattered debris, and the marked cellular infiltration. Hematoxylin and eosin stain; ×60.

results obtained are, as they seem to be, a fair cross-section of all cases of ulcer, they show that the overwhelming number of patients suffering from peptic ulcer harbor such septic foci. In all but one of all cases of ulcer examined, there was one or more definite infective focus in the body at the time the patient registered; from these, streptococci were isolated that produced lesions in the stomach or duodenum of rabbits when injected intravenously. On the other hand, in only comparatively few instances were micro-organisms cultured from infective foci in cases other than those of peptic ulcer localized in the stomach and duo-

denum; when they did localize there, the lesions were fewer in number and were not nearly as pronounced.

That the appendix, gallbladder, colon, sinuses or bronchi may also become foci of infection for the streptococcus of the ulcer-producing type is possible, especially if the ulcer persists after other foci have been eradicated. However, our study does not include these foci, because they are generally secondary to some other focus. The foci we did study often looked innocent and were clinically mild, and it was impossible to determine by perception, palpation or roentgen-ray examination which focus harbored the ulcer-producing organism. Mere objective clinical examination of a supposed focus is of little importance in determining which organism a focus contains. No one is able to tell definitely

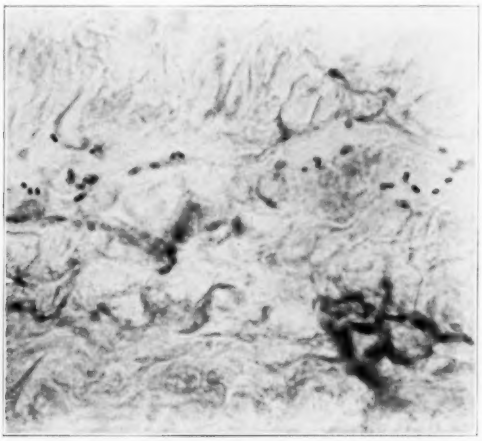

Fig. 8.—Diplococci scattered in the submucosa adjacent to the smaller blood vessels near the muscularis mucosa of the ulceration shown in figure 7. Gram-Weigert stain; × 1000.

from the appearance of a tonsil, the roentgenogram of a devitalized tooth or the palpation of a prostate what kind of organisms are harbored therein or to state their biologic characteristics. An actual culture is the best known method for determining these facts; even by this method buried tonsil tags, root tips or residual areas in edentulous mouths are overlooked unless watched for carefully, because the local clinical symptoms are generally absent or mild.

In order to evaluate the usual surgical and medical treatment when combined with removal of infective foci and sometimes the use of an autogenous vaccine, a questionnaire was sent to eighty of our patients from seven to twelve months after their dismissal from the hospital in

order to ascertain their general health, the presence or absence of digestive distress and their cooperation in the eradication of any remaining foci of infection. Fifty-three replies were received and tabulated. Although generalizations cannot be deduced from such a comparatively small series, there are some results that deserve consideration.

In the cases in which medical treatment was carried out, the ulcers were acute or bleeding, while in the cases in which operation was performed, the ulcers were of a more chronic type. There was practically as much improvement following medical management as following major operations. In the group of thirty-seven cases in which all known foci of infection had been eradicated, the general health had improved; twenty-nine patients reported themselves as well and eight as in fairly good health with some gastric distress at times. There were eight patients treated either medically or surgically, only part of whose infective foci had been eradicated; at the time of the questionnaire, two of these patients were well, five were in fair health and one was unimproved. Of the eight patients who received either surgical or medical treatment but did not cooperate with our request to have evident infective foci removed, only one was well, three were in fairly good health and four stated that they were unimproved. Thus in the majority of cases of peptic ulcer, there were definite foci of infection which contained streptococci having definite affinity for the stomach and duodenum; in the majority of cases in which such foci were eradicated, the patient was well and free from symptoms from seven to twelve months later.

Autogenous vaccine was given to seven patients. One of the seven was not benefited by it after using it for several months; he, however, had neglected to have septic tonsils removed. Of the remaining six, the septic tonsils of one were removed only two months before this article was written, and he is in fairly good condition; the other five are enjoying good health.

SUMMARY AND CONCLUSIONS

1. Foci of infection bear a definite etiologic relationship to primary and recurring peptic ulcers; they are found in almost every case of peptic ulcer, and they have been shown to contain the causative streptococcus.

2. The favorable results obtained by the removal of foci of infection in some cases of peptic ulcers which recurred repeatedly after surgical management indicate that this procedure will help to prevent recurrence.

3. The foci in the teeth, tonsils and prostate which were studied were often obscure and innocent-looking and generally did not produce local symptoms.

4. Devitalized, roentgenologically-negative teeth, act as a focus of infection as often as roentgenologically-positive teeth, according to our experimental results.

5. The causative streptococcus has been demonstrated in and isolated from the resected ulcer of man as well as from the foci of infection and has produced, electively, similar lesions of the stomach and duodenum when injected intravenously into rabbits.

6. The streptococcus which we have isolated consistently in these cases is identical with that first described by Rosenow as having etiologic importance in the production of peptic ulcer in man, and it provides a means for active immunization with specific autogenous vaccine.

SUBLINGUAL ABSORPTION OF DRUGS: MORPHINE

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Paulson,[1] being impressed by the accessibility, the thin mucous membrane and the abundant blood supply of the sublingual space, was one of the first to recommend the sublingual administration of drugs. His experience led him to believe that drugs were rapidly absorbed when administered in this manner. Other clinicians have held the same view, and recently Fantus [2] has advocated the use of this method. But what evidence is there that drugs are readily absorbed from this space?

As far as we know, quantitative studies to determine the selective absorption capacity of this membrane have not been made. The claims found in the literature are, for the most part, based on clinical impressions. It is known that the effects of certain drugs are manifest soon

Quantity of Drug Recovered After Sublingual Administration

Experiment Number	Quantity of Drug, Mg.	Time for Absorption, Minutes	Amount Recovered, Mg.	Per Cent Recovered
1	15	5	13.5	90
2	15	10	9.9	66
3	10	10	6.5	65
4	10	10	8.1	81
5	10	10	7.0	70
6	10	10	7.0	70
7	10	10	7.5	75

after their sublingual administration; at times, for example, the effects of nitroglycerine seem to appear within a few seconds after its introduction. Atropine and morphine, given the same way, usually act after a few minutes. In such instances, it is difficult to say how the drug entered the circulation. Seconds of distaste seem long to the patient, and the saliva with the drug is often swallowed soon after the drug is administered. The favorable effects are then due to intestinal absorption, and these may appear early with certain drugs.

Bachem,[3] Mendel,[4] Tracy [5] and others have claimed selective absorption properties for the sublingual and oral mucous membranes, but they

1. Paulson, W.: Sublingual Medication, Practitioner **97**:389 (Oct.) 1916.
2. Fantus, B.: The Technic of Medication, J. A. M. A. **87**:32-33, (July 3) 1926.
3. Bachem: Resorption von Arzneimitteln in der Mundhole, Klin. Wchnschr. **3**:461 (March 11) 1924.
4. Mendel, F.: Die perlinguale Application der Medikamente, München. med. Wchnschr. **69**:1593 (Nov. 17) 1922.
5. Tracy, E. A.: A Bit of Hormonology, with Practical Applications, Medicine and Surgery, January, 1918, p. 38.

have not offered sufficient evidence. Conclusions were drawn from clinical impressions and unsatisfactory experiments. The need for more definite information in a subject of practical importance suggested the present investigation. The study was conducted as follows: A known amount of drug was placed beneath the tongue in the sublingual space, and after a given length of time, the contents were washed out and studied quantitatively to determine the exact amount of drug unabsorbed. This test is simple and gives definite information.

We used this technic in making studies with morphine sulphate. The results show that morphine sulphate in the form ordinarily administered is not appreciably absorbed by the sublingual mucous membrane. In seven experiments in which quantities of 10 and 15 mg. of powdered morphine sulphate were placed under the tongue for periods of five and ten minutes, from 65 to 90 per cent of the drug was recovered. Allowing for loss both in recovery from the mouth and in the determination, we would estimate that probably less than 10 per cent, if any at all, of the total drug was absorbed.

TECHNIC AND METHOD

The quantitative determination of morphine was made according to the method outlined by Gauss,[6] which employs the Marquis reagent [7] for the quantitative estimation by means of a colorimeter. This reagent is prepared by adding one part of formaldehyde, U. S. P., to 20 parts of concentrated sulphuric acid. When added to the smallest perceptible amount of pure dry morphine, it immediately gives an intense purplish blue color. This delicacy makes it well suited for quantitative use. When the morphine is nearly pure, extraction is unnecessary, and a direct determination can be made, as follows: Prepare a standard by evaporating an aqueous solution containing exactly 1 mg. of morphine sulphate to dryness. In the same way, prepare the unknown in approximately 1 mg. amounts. To each evaporating dish pipet 10 cc. of freshly prepared Marquis' reagent, and thoroughly mix the coloring by scraping the morphine from the sides of the dish with a glass rod. Match the unknown against the standard in a Dubosq colorimeter.

Impurities, particularly coloring matter, necessitate preliminary extraction, which is accomplished with trichloracetic acid and chloroform.[6] In this way, a high percentage of the alkaloid can be recovered, the amount depending on the quantity of morphine present, and the amount and character of the material from which it is extracted.[8]

6. Gauss, H.: Colorimetric Method for Estimation of Morphine in Colloidal Mixtures and Tissues, J. Lab. Clin. Med. **6**:699, 1920-1921.

7. Marquis, Eduard: Arb. des Pharm. Inst., Dorpat, 1896, no. 14, p. 117.

8. Hatcher, R. A., and Davis, D.: The Excretion of Morphine Into the Stomach, J. Pharmacol. & Exper. Therap., August, 1925, no. 1, vol. 26.

The saliva collected in each experiment varied from 1 to 5 cc., and as only one fifth or one tenth of this was used for a determination, the impurities were too small appreciably to affect a direct estimation. Less than 0.5 cc. of pure saliva usually lowers the reading of 1 mg. of pure morphine sulphate by 0.1 mg. (10 per cent). This amount of saliva usually produces a slight greenish tinge to the blue coloration, but intensities are easily matched, and in some experiments the colors were almost exact. Equivalent amounts of pure saliva were added to each standard, as a control. It was then unnecessary to extract with chloroform, which, in itself, would entail some loss.

The subjects for these experiments possessed clean mouths and healthy gums. Before each determination, the teeth were brushed and the mouth rinsed with distilled water. An exact quantity of morphine sulphate was placed in the sublingual space, and after an interval of five or ten minutes, the contents were drooled into a receptacle and the mouth rinsed with a known amount of water which was added to the original contents. A small loss is unavoidable as some saliva is swallowed.

CONCLUSIONS

1. The absorption capacity of the sublingual mucous membrane was studied by introducing a known amount of morphine sulphate beneath the tongue, and later analyzing the contents of the mouth to determine the exact amount of drug unabsorbed.

2. The results of these studies show that morphine sulphate, in the form ordinarily administered, is not appreciably absorbed by the sublingual mucous membrane.

3. A review of the meager literature on this subject failed to reveal sufficient evidence to support the notion that the sublingual mucous membrane has the capacity to absorb drugs rapidly. On the contrary, the results with morphine sulphate, which is readily soluble in water and quickly absorbed from gastro-intestinal and rectal mucous membranes, suggest that allied drugs are also little absorbed by the sublingual membrane.

4. The sublingual administration of morphine should be discontinued.

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CHEMICAL CHANGES IN THE BLOOD IN MERCURIC CHLORIDE POISONING

MECHANISM AND SIGNIFICANCE OF HYPOCHLOREMIA *

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A marked reduction of the blood chlorides may occur in any patient suffering from mercury poisoning. In his fatal cases of poisoning with mercuric chloride, Heim [1] observed a lower concentration of blood chlorides than in any other condition, the lowest figure being 210 mg. sodium chloride per hundred cubic centimeters of blood. In his discussion of theories to explain the condition, he concluded that the hypochloremia could not be explained by a loss of chlorides from the intestinal tract either by vomiting or by diarrhea. As an alternate possibility, he offered the view that a specific poisoning of vascular membranes or a physiochemical change in the blood permits a loss of sodium chloride directly into the tissues.

Data in proof of either theory have not been offered, and we feel that a metabolic change of such fundamental importance merits experimental investigation. With this point in view, we have studied the chemical changes in the blood of dogs and rabbits following the intravenous injection of mercuric chloride.

EXPERIMENTS

In the course of these studies, twenty-two dogs and seven rabbits were killed. A stock solution of mercuric chloride, 1 per cent in distilled water, was prepared for intravenous injection. The size and number of doses were varied sufficiently to give a complete check on results. All injections were given carefully and slowly to prevent circulatory accidents and to avoid the confusion of sudden or unusual toxic effects. The several protocols and tables, selected for detailed study, demonstrate

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* From the Department of Surgical Pathology, Indiana University School of Medicine, the Eli Lilly Research Fellowship.

* This experimental work was made possible through the courtesy of Dr. W. D. Gatch.

* The chemical analyses were done in the department of Biochemistry under the supervision of Dr. B. B. Turner and Dr. R. N. Harger.

1. Heim, F.: Hypochloremia in Poisoning with Mercuric Chloride, Schweiz. med. Wchnschr. **55**:1085 (Nov. 26) 1925.

the results consistently obtained in each series of experiments. Further reduplication of data is considered unnecessary.

TOXICITY OF MERCURIC CHLORIDE INJECTED INTRAVENOUSLY INTO DOGS

Dogs showed marked variation in their individual reaction to mercury poisoning by this method. Our experiments have shown that a single intravenous dose of 1 mg. of mercuric chloride per kilogram of body weight may not produce any significant change in the normal dog. However, a dog of reduced vitality may develop a violent intoxication and die within a week following such an injection. A dose of 4 mg. per kilogram is uniformly fatal in about three days' time. Injections of 2 and 3 mg. per kilogram are fatal after an interval which may vary from six days to six weeks. Repeated small injections are similarly fatal. The various changes which occur are considered in detail throughout the following discussion.

TABLE 1.—*Results of Intravenous Injection of Mercuric Chloride into Dog 1* *

Day	Mg. per 100 Cc. of Blood		
	Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen
0	470.3	15.2	36.0
2	437.3	....	37.5
20	456.0	33.1	88.2
38	461.0	20.2	48.0

* No significant changes followed a single intravenous injection of 1 mg. of mercuric chloride per kilogram of body weight.

SUBACUTE MERCURIAL POISONING

In the slowly developing intoxication which ordinarily follows the smaller injections of mercury, only a gradual reduction in the function of the kidney is observed, as shown by the slow accumulation of nitrogenous elements in the blood. Vomiting and marked diarrhea do not occur, nor a significant change in the blood chlorides. There is salivation, loss of appetite, loss of weight and lethargy, from which state the animal may recover or may lapse into a fatal coma.

DOG 1 (table 1).—A vigorous animal, weighing 22 Kg., received by intravenous injection 2.2 cc. of 1 per cent solution of mercuric chloride (1 mg. per kilogram). With the exception of slight diarrhea and mild salivation in the first few days, the animal appeared normal. There was a temporary reduction in weight, but after six weeks the dog appeared to have entirely recovered.

DOG 2.—A healthy young animal weighing 10 Kg. received injections of mercuric chloride as indicated in table 2. The dog was penned in a metabolism cage and allowed as much water as he wanted but no food. Excretions were analyzed to determine sodium chloride output. The animal appeared essentially normal for fourteen days, during which time he had received five injections of 0.6 mg. mercuric chloride per kilogram and two injections of 1.25 mg. per kilo-

gram. On the nineteenth day, however, following an injection of 2.5 mg. per kilogram, he lapsed into coma and died on the twenty-first day. Histologic examination of the kidneys showed the early changes of acute tubular nephritis.

From a study of the first two protocols and tables, it will be noted that dog 1, following a single intravenous injection of 1 mg. mercuric chloride per kilogram, showed only a temporary slight increase in the nitrogenous elements of the blood. He did not vomit, and there was no change in the blood chlorides. Likewise, dog 2 endured seven small injections of mercuric chloride over a period of two weeks. During this time the chemical changes in the blood were only those of starvation. The sodium chloride excretions in the urine were those of a starving animal; vomiting did not occur, and there were no changes in the blood chlorides. On the seventeenth day, however, he received an intravenous injection of 2.5 mg. mercuric chloride per kilogram. In the twenty-four

TABLE 2.—*Result of Intravenous Injections of Mercuric Chloride Into Dog 2**

	Intravenous Injections of Mercuric Chloride,	Mg. per 100 Cc. of Blood			Urine		Vomitus	
Day	Mg. per Kg. of Body Weight	Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen	Volume, Cc.	Sodium Chloride, Gm.	Volume, Cc.	Sodium Chloride, Gm.
0	0.6	459	20.5	43.8	.....	...	.....	...
3	0.6	459	13.4	40.0	1,350	2.9	None	...
5	0.6	480	12.2	36.6	.....	...	.....	...
7	0.6	458	10.6	28.6	700	1.1	None	...
9	0.6	435	11.6	26.4	.....	...	.....	...
12	1.25	440	9.8	33.7	560	0.7	None	...
14	1.25	462	6.2	31.9	90	0.2	None	...
17	2.5	462	10.2	32.5	180	0.4	None	...
18	None	440	34.8	65.0	None	...	500	2.7
19	None	372	43.6	98.3	None	...	None	...
21	At death	429	191.6	339.6	None	...	None	2.5†

* Multiple small injections of mercuric chloride were given intravenously.
† Washings from pen.

hours which followed there was 500 cc. of vomitus, the titration of which yielded 2.7 Gm. of sodium chloride. The additional 2.5 Gm. recovered in the final washing of the pen must also have been chiefly the result of this vomiting. Accompanying this, there was a sharp reduction in the blood chlorides. Further losses of chloride did not occur, and the sodium chloride content of the blood again rose, conceivably owing to absorption from the tissues. In addition to this change, the terminal blood showed the nitrogen accumulation of complete urinary suppression.

ACUTE MERCURIAL POISONING

Acute rapidly fatal mercurial poisoning is characterized by a sudden suppression of urine, a rapid accumulation of nitrogenous elements in the blood, and acidosis as shown by a marked reduction of the carbon dioxide combined in the plasma and violent intoxication. Accompanying this, there was an excessive loss of chlorides through vomiting and a marked reduction in the sodium chloride of the blood.

Dog 17 (table 3).—During the previous three months, this animal had been subjected to deep ether anesthesia on three occasions for experimental study. Finally, the gallbladder was removed. He appeared normal, well nourished and healthy. As he weighed 19 Kg., he received a single intravenous injection containing 19 mg. of mercuric chloride (1 mg. per kilogram). His reaction was the violent intoxication characteristic of a much larger dose. He was dead at the end of six days.

Dog 3 (table 4).—A healthy animal weighing 16 Kg. received four intravenous injections of 20 mg. of mercuric chloride at forty-eight hour intervals. This dog was penned in a metabolism cage and allowed as much water as he wanted but no food. There was a sharp terminal reduction in the sodium chloride of the blood immediately following an excessive loss of chlorides by vomiting.

TABLE 3.—*Unusual Reaction of Dog 17 to the Intravenous Injection of Mercuric Chloride*

	Mg. per 100 Cc. of Blood			Output in Vomitus, No Urine	
Day	Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen	Volume	Sodium Chloride, Gm.
0	481	31.2	41.9	.....	...
3	387	117.6	170.4	1,300	7.5
6	271	203.6	403.6	730	4.1
At death					

TABLE 4.—*Marked Reduction of Blood Chlorides Following an Attack of Excessive Vomiting as a Result of Intravenous Injection of Mercuric Chloride Into Dog 3*

	Intravenous Injections of	Mg. per 100 Cc. of Blood			Carbon Dioxide	Urine		Vomitus	
Day	Mercuric Chloride, Mg. per Kg.	Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen	Combined in 100 Cc. of Plasma	Volume, Cc.	Sodium Chloride, Gm.	Volume, Cc.	Sodium Chloride, Gm.
0	1.25	459	14.0	39.0	54 cc.	.....	...	.....	.....
2	1.25	470	78.9	130.5	36 cc.	1,200	2.5	None	None
4	1.25	435	157.2	226.4	27 cc.	400	0.5	None	None
6	1.25	412	230.4	449.8	.....	None	None	None	None
8	At death	183	334.4	555.0	36 cc.	None	None	1,010	7.8

Necropsy on the eighth day showed a marked destruction of the renal tubules and necrosis of the liver. In the last two days of life, tetany was a marked symptom.

Dog 9 (table 5).—An intravenous injection was given of 2.5 mg. of mercuric chloride per kilogram. The dog was penned in a metabolism cage for the collection of sodium chloride excretion, allowed as much water as he wanted but no other food. A reduction of blood chlorides followed an excessive loss of sodium chloride by vomiting in the last four days. The dog died of tetany. Analysis of the liver and muscle showed a reduction of the sodium chloride in these tissues. Necropsy on the eighth day showed cloudy swelling in the parenchymatous tissues and the typical necrosis of renal tubules.

Dog 6 (table 6).—One intravenous injection of 4 mg. of mercuric chloride per kilogram. The typical rapidly fatal intoxication followed. Necropsy on the third day showed total destruction of the convoluted tubules in the kidney and acute parenchymatous degeneration in all other tissues. The chloride losses are indicated in the table.

An analysis of the foregoing protocols and tables reveals three main factors contributing to the fatal course of mercuric chloride poisoning.

1. Following a massive dose of the poison, a generalized intoxication is rapidly fatal. The chemical changes which occur in the blood during this interval are insufficient to account for the early death. The fatal mechanism in this case must be direct injury to vital centers.

2. Following doses of less toxicity, the chief damage occurs in the convoluted tubules of the kidney. Other things remaining equal, the rapidity of the fatal course is proportional to the reduction of renal function which results from this damage to the kidney.

TABLE 5.—*Results of Intravenous Injection of 2.5 Mg. of Mercuric Chloride Per Kilogram Into Dog 9*

	Mg. per 100 Cc. of Blood			Urine		Vomitus	
Day	Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen	Volume, Cc.	Sodium Chloride, Gm.	Volume, Cc.	Sodium Chloride, Gm.
0	479	33.0	61.2	...	...	.....	...
2	524	53.2	89.8	200	0.5	800	3.0
4	506	108.0	154.6	160	0.1	270	1.2
8	287	430.6	600.1	None	None	1,470	12.1
At death							

Sodium chloride in tissues: liver, 1.4 Gm. per Kg.; muscle, 0.73 Gm. per Kg.

TABLE 6.—*Result of Intravenous Injection Into Dog 6, Followed by Fatal Intoxication on the Third Day* *

	Mg. per 100 Cc. of Blood			Carbon Dioxide Combined in 100 Cc. Plasma		Vomitus	
Day	Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen		Urine	Volume, Cc.	Sodium Chloride, Gm.
0	543	24.0	48.0	52 cc.	.....	...	...
2	384	107.0	170.0	33 cc.	None	930	8.0
3	316	143.2	181.8	24 cc.	None	200	2.4
At death							

* One intravenous injection containing 4 mg. mercuric chloride per kilogram.

3. There is a severe gastro-intestinal irritation which in dogs results in excessive losses of chlorides through vomiting. Accompanying this loss there is a reduction in the sodium chloride in the blood. The gastric tetany which results may of itself be fatal. In these experiments we have never observed a marked reduction of the sodium chloride in the blood which was not explained by losses of chloride from vomiting.

Our experiments with rabbits supply additional evidence of this relationship. As the rabbit is an animal that does not vomit, avenues for excessive loss of chloride from the body are not found. It is significant that acute mercury poisoning in rabbits is not accompanied by any marked reduction in the sodium chloride of the blood.

In these studies of animals it has been evident that the reduction of blood chlorides results directly from loss of chloride through vomiting, and not from any obscure toxic change in the blood or its vessels. This view is in keeping with the conclusions set forth in a previous publication [2] concerning the hypochloremia of acute intestinal obstruction.

SIGNIFICANCE OF HYPOCHLOREMIA IN MERCURY POISONING

The vomiting which we have observed in these dogs results not only from gastro-intestinal irritation by the poison, but also as a symptom of

TABLE 7.—*Results of Intravenous Injection of 3 Mg. of Mercuric Chloride Per Kilogram Into Three Rabbits*

Rabbit Number	Day	Mg. per 100 Cc. of Blood	
		Sodium Chloride	Total Nonprotein Nitrogen
4	0	445.5	33.9
	3	435.0	385.4
	4 at death	478.0	454.5
5	0	463.6	41.6
	3	435.6	315.6
	4 at death	495.0	438.0
7	0	453.7	47.6
	3	417.4	220.5
	4	445.5	265.5

TABLE 8.—*Results of Intravenous Injections of 4 Mg. of Mercuric Chloride Per Kilogram and Hypodermic Injection of Salt Solution*

Day	Comment	Mg. per 100 Cc. of Blood			Carbon Dioxide Combined in 100 Cc. Plasma	Urine		Vomitus	
		Sodium Chloride	Urea Nitrogen	Total Non-protein Nitrogen		Volume, Cc.	Sodium Chloride, Gm.	Volume, Cc.	Sodium Chloride, Gm.
0	.....	480.7	23.0	45.5	48 cc.	...	...	...	...
1	.....	389.1	35.6	86.1	.....	370	1.3	300	4.6
3	Dog in severe tetany relieved by 1,000 cc. 1% sodium chloride hypodermically.	306.0	155.0	266.5	21.1 cc.	None	None	700	4.3
4	500 cc. 1% sodium chloride.....	412.0	167.0	234.0	.....	None	None	None	None
5	Dog dying.....	496.0	262.0	410.0	26.8 cc.	None	None	500	6.0

urinary suppression. As the senior author [2] has previously shown, dogs vomit excessively following the removal of both kidneys or ligation of both ureters. The significance of the reduction in blood chlorides will be considered in detail.

DOG 5 (table 8).—Dog 5 received intravenous injections of 4 mg. of mercuric chloride per kilogram. At the end of three days, he was dying in a state of tetany. This symptom was relieved entirely by hypodermic administration of

2. Gatch, W. D.: Trusler, H. M., and Ayres, K. D.: Acute Intestinal Obstruction: Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, Am. J. M. Sc. **173**:649 (May) 1927.

1,000 cc. of 1 per cent sodium chloride. There was a marked temporary improvement. The animal lived for two more days. The blood chloride remained normal, and tetany did not return. Necropsy on the fifth day showed the typical changes of mercury poisoning.

This experiment brings out one point which we wish to emphasize strongly. In the past, many have held the view that gastric tetany is always associated with a state of alkalosis, as shown by an increase in the carbon dioxide combined in the plasma. In dogs with mercury poisoning, the blood invariably shows a state of acidosis. Nevertheless, these animals all exhibit marked tetany as the sodium chloride in the blood falls below 300 mg. per hundred cubic centimeters. As is shown in table 8, the tetany is relieved at once by restoration of the blood chloride level.

TABLE 9.—*Results of Intravenous Injections of 4 Mg. of Mercuric Chloride Per Kilogram Into Dog 7; Sodium Chloride was Also Administered*

Day	Intravenous Injections of 2% Sodium Chloride, Cc.	Mg. per 100 Cc. of Blood			Urine		Vomitus	
		Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen	Volume, Cc.	Sodium Chloride, Gm.	Volume, Cc.	Sodium Chloride, Gm.
0	500	525	30.1	57.0	...	...	.....	....
1	500	427	60.5	111.0	480	2.0	2,280	14.5
2	500	506	101.2	159.4	370	0.7	2,460	5.2
3	500	552	120.6	166.6	70	0.4	1,960	6.4
4	500	570	131.8	180.7	130	0.7	830	4.2
5	500	551	193.2	192.8	100	0.7	1,860	5.1
7	None	448	224.0	225.0	None	None	2,430	7.9
8	At death	472	230.0	306.0	None	None	1,600	9.0

Liver, 2.5 Gm. sodium chloride per Kg.; muscle, 1.3 Gm. sodium chloride per Kg.

We conclude, therefore, that gastric tetany is a symptom of hypochloremia without direct relationship to the concentration of the carbonate buffer substances in the blood.

The hypochloremia is easily relieved or prevented by the administration of sodium chloride solution. The accompanying protocols and tables demonstrate, however, that this measure is of secondary importance in mercury poisoning.

Dog 7 (table 9).—Dog 7 received 4 mg. of mercuric chloride per kilogram, together with 500 cc. of 2 per cent salt solution intravenously. During the next five days, he received five more intravenous injections of 500 cc. of 2 per cent salt solution. He lived eight days. Necropsy showed the typical changes of severe mercury poisoning.

As shown in table 10, dog 14 received intravenously a sufficient amount of 1 per cent salt solution to maintain a safe level of blood chlorides, but he was not benefited thereby. His course was practically the same as that of dog 15, which did not receive any treatment. These animals received 2 mg. of mercuric chloride per kilogram and lived seven and six days, respectively. Dog 7, table 9, received 4 mg. of mercuric

chloride per kilogram (a dose uniformly fatal in the untreated animal in three days). In the first five days, however, this dog received six intravenous injections of 500 cc. of 2 per cent sodium chloride solution. By far the greater part of this salt was lost through vomiting. The treatment did, nevertheless, maintain kidney excretion for five days. The rate of nitrogenous accumulation in the blood was markedly slowed, and the animal lived for eight days. This favorable action on an overwhelming dose of the poison may be taken to indicate therapeutic value in the treatment. It seems possible that with a less massive dose of mercury, life might be saved by repeated intravenous administration of hypertonic salt solution. As we have previously stated, animals show marked variation in their reaction to small doses of mercuric chloride, and for this reason we do not have conclusive proof of this therapeutic action.

TABLE 10.—*Results of Intravenous Injections of 2 Mg. of Mercuric Chloride Into Dogs 14 and 15*

Dog	Day	Intravenous Injections of 1% Sodium Chloride, Cc.	Mg. per 100 Cc. of Blood		
			Sodium Chloride	Urea Nitrogen	Total Nonprotein Nitrogen
14	0	500	519.7	30.1	58.8
	1	500	.....	.....	.....
	2	500	407.0	80.2	108.4
	4	500	453.7	150.6	222.2
	7	At death	463.6	230.4	324.3
15	0	No treatment	500.0	12.4	40.5
	2	No treatment	351.4	70.2	142.8
	4	No treatment	343.2	170.4	214.2
	6	No treatment	240.9	245.4	376.2

CLINICAL APPLICATIONS

The foregoing results seem to indicate that hypochloremia should be an important consideration in mercury poisoning. However, it must be remembered that dogs are animals which secrete a high concentration of hydrochloric acid into the stomach. Furthermore, they are inclined to evacuate the stomach by vomiting at the least provocation. This tendency no doubt makes them much more susceptible to a severe degree of hypochloremia than the average human patient. During the course of our experiments, we did, however, observe one patient in whom there were significant changes in the blood chlorides.

A woman of 20 years had placed a 7½ grain (0.49 Gm.) tablet of mercuric chloride in the vagina four days before admission to the hospital. There was a total suppression of urine, slight generalized edema, tenesmus and diarrhea and occasional vomiting. The blood contained 193 mg. of urea and 416 mg. of sodium chloride per hundred cubic centimeters. She was given daily gastric lavage and colonic irrigations of 5 per cent sodium bicarbonate. Other treatment need not be discussed at this time. After three days in the hospital, the urea had increased to 338 mg., and the sodium chloride had fallen to 368 mg. per hundred cubic

centimeters of blood. Thereafter, she was given daily intravenous transfusions of normal salt sufficient to maintain the blood chloride level above 400 mg. per hundred cubic centimeters. Her general condition was improved by this measure, but urinary suppression remained absolute until the twelfth day. Following decapsulation of the right kidney on this day, there was an excretion of 900 cc. of urine. Following decapsulation of the other kidney on the fourteenth day, there was a slight reduction of nitrogenous elements in the blood, and the daily output of urine remained above 500 cc. Death on the twentieth day seemed to result chiefly from a severe pelvic infection due to the extensive necrosis and sloughing of the external genitalia.

There are several points of interest in this case, but we are concerned chiefly with the changes in the blood chlorides. Though the hypochloremia was not allowed to become marked in this patient, it is certain that the reduction was too great to be accounted for by vomiting. We believe that the loss in this case was brought about by colonic irrigations and gastric lavages with alkaline solutions. The significance of this is evident. In any condition which calls for routine lavage of the stomach or the intestinal tract, the danger of reducing the blood chlorides should be borne in mind. The danger can no doubt be mitigated by including physiologic sodium chloride as a component of such solutions.

We believe that any marked reduction of the blood chlorides is to be explained by loss from the gastro-intestinal tract. In the case which we have cited, one other factor may have been responsible for the constant tendency to hypochloremia. This patient showed a mild but progressive generalized edema. This constant transudation of serous fluid must carry sodium chloride from the blood, and if disturbed alimentation prevents the intake of salt, a reduction of blood chlorides must occur.

We have seen this mechanism strikingly demonstrated in a woman suffering from cirrhosis of the liver. The terminal exacerbation of her portal obstruction caused anasarca and a rapid accumulation of ascitic fluid (from 2 to 6 liters were removed daily by paracentesis). After several days, she showed symptoms of tetany. The sodium chloride in the blood was found to be 340 mg. per hundred cubic centimeters. It is apparent that a rapid transudation of fluid from the blood may produce a significant reduction of the chlorides.

In the human patient poisoned with mercury, the tendency to edematous accumulations in the tissues may be a factor in producing hypochloremia. We feel, however, that the chief cause is loss of chlorides from the gastro-intestinal tract.

GENERAL SUMMARY AND CONCLUSIONS

1. Dogs poisoned by intravenous injections of mercuric chloride suffer a marked reduction in the sodium chloride of the blood, due to loss of chlorides through vomiting.

2. This hypochloremia, though associated with a relative acidosis, produces gastric tetany. The tetany, therefore, is not a symptom of alkalosis, but occurs in any condition of hypochloremia without direct relationship to the carbon dioxide combined in the plasma.

3. Restoration of the blood chloride level relieves and prevents tetany but does not otherwise modify the course of mercury poisoning. There is some evidence that 2 per cent salt solution administered intravenously may be of value by forcing excretion from the kidney.

4. In the human patient poisoned with mercury, the danger of a low level of blood chlorides should be borne in mind. Other clinical applications have been discussed.

THE INFLUENCE OF ALKALIS ON THE SECRETION AND COMPOSITION OF GASTRIC JUICE

III. THE EFFECT OF SODIUM BICARBONATE ON THE GASTRIC RESPONSE TO HISTAMINE *

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Various writers have stated that the antacid effect of sodium bicarbonate depends not only on the direct neutralization of hydrochloric acid, but also on a reduction of the amount of acid secreted in the stomach. For massive doses of the salt, this depression of gastric secretion was confirmed in some previously published experiments of mine.[1] The minimum amount of bicarbonate which could be depended on to produce this effect, however, was found to be about 1 Gm. per kilogram of body weight, whether given as a single dose after a meal, or as the total daily dose for dogs on prolonged feeding with alkali. With smaller doses of bicarbonate, within the limits of ordinary antacid medication, the secretory response to a meal was on the average slightly greater than that found in the control experiments.

If the human stomach is as little affected by alkalis as is that of the dog, depression of secretion is probably not a factor in any therapeutic action which sodium bicarbonate may have. If this is given to an adult, the minimum daily amount which might be expected to reduce secretion would be from 50 to 75 Gm. Keefer and Bloomfield [2] have recently found that doses of from 1 to 2 Gm. do not have any apparent effect on secretion in man.

In the present investigation, I have again studied the effect of single doses of bicarbonate, using amounts considerably greater, in proportion to body weight, than those given by Keefer and Bloomfeld to human subjects. Instead of food as a gastric stimulant, a standard dose of histamine (1 mg. of the dihydrochloride) was injected subcutaneously. This procedure gives a response which is more constant quantitatively than that obtained from repeated feeding of a standard meal.[3]

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* From the Department of Physiology and Pharmacology, Loyola University School of Medicine.

1. Boyd, T. E.: The Influence of Alkalies on the Secretion and Composition of Gastric Juice: I. The Effect of Prolonged Administration of Sodium Bicarbonate and Calcium Carbonate, Am. J. Physiol. **71**:455 (Jan.) 1925; II. The Effects of Single Doses of Sodium Bicarbonate and Calcium Carbonate, ibid., p. 465.

2. Keefer, Chester S., and Bloomfield, A. L.: A Quantitative Study of the Effect of Sodium Bicarbonate on Gastric Secretion, Bull. Johns Hopkins Hosp. **39**:379 (Dec.) 1926.

3. Lim, R. K. S.: On the Relation Between the Gastric Acid Response and the Basal Secretory Rate in the Stomach, Am. J. Physiol. **69**:318 (July) 1924.

Some work has also been done to determine whether or not the alkali affects secretion locally by contact with the gastric mucosa. In the experiments referred to in this paper,[1] the bicarbonate was in all instances fed by mouth, and the juice was collected from a separated pouch. Pavlov's work indicates that the secretion of the pouch parallels that of the main stomach, but this relation may not hold true under all conditions.

EXPERIMENTAL WORK

Administration of Bicarbonate by Mouth.—Two Pavlov pouch dogs were used, the weights being respectively 10.2 and 11.4 Kg. During the experimental periods they were kept on a diet of milk and white bread. The alkali was given in 2.5 or 5 per cent solution of water, by a stomach tube. When this involved giving more than 200 cc. of liquid, it was

TABLE 1.—*Cubic Centimeters of Gastric Juice Collected After the Administration of 1 mg. of Histamine Dihydrochloride*

	Weight, Kg.	Controls	10 Gm. Sodium Bicarbonate in 400 Cc. Water	10 Gm. Sodium Bicarbonate in 200 Cc. Water	10 Gm. Sodium Bicarbonate in 200 Cc. with Water ad lib.
Dog 40.....	10.2	15.0	22.3	6.0	19.7
		23.0	23.3	11.2	15.0
		18.3	18.7	7.9	12.5
		20.1	....	11.5	15.5
		22.1	....	....	....
		20.7	....	....	....
		18.7	....	....	....
Mean.....		19.7	21.1	9.2	15.7
Dog 38.....	11.4	17.0	19.7	10.3	16.8
		18.2	17.5	12.1	19.0
		21.0	23.2	13.3	19.4
		17.2	23.0	....	13.5
		18.5	....	....	....
Mean.....		18.4	20.9	11.9	17.2

divided into two or more portions, given one hour apart. The histamine was administered one hour after the last dose of alkali, and the gastric juice was collected for two hours following. The secretion in response to the same dose of histamine was measured in control experiments without bicarbonate. Experiments were preceded by a period of from twelve to sixteen hours during which the animals were kept without food or water, and none were carried out when the resting or continuous secretion exceeded 4 cc. per hour. An interval of at least forty-eight hours was allowed between the injections of histamine.

It was found (table 1) that the giving of 10 Gm. of sodium bicarbonate (approximately 1 Gm. per kilogram of body weight) in 2.5 per cent solution did not produce any diminution in the amount of juice secreted after an injection of histamine. The acidity of the juice (not shown in the tables) likewise remained undiminished, always being near the maximum figure of 0.45 to 0.5 per cent free hydrochloric acid.

When the same dose of alkali was given in 5 per cent solution, without additional water, the secretion was reduced (column 3 in table 1). The procedure was then repeated, water being left in the cages for the animals to drink at will. The secretion was increased until it almost equaled the average obtained in the control experiments (column 4, table 1).

Because of this difference in effect between the dilute and concentrated solutions, it seemed likely that the latter acted through some influence on the water supply to the gastric glands. According to this hypothesis, a saline cathartic in concentrated solution might be expected to have a similar depressing effect on secretion. Table 2 shows the result of administering histamine one hour after the giving of 15 Gm. of magnesium sulphate in 100 cc. of water.

TABLE 2.—*Cubic Centimeters of Gastric Juice Collected After the Administration of 1 mg. of Histamine Dihydrochloride. Experimental Conditions Described in Text*

	Weight, Kg.	20 Gm. Sodium Bicarbonate Water ad lib.	15 Gm. Magnesium Sulphate 100 Cc. Water	Irrigation of Pouch with Sodium Bicarbonate Solution
Dog 40	10.2	5.2	10.1	26.2
		2.0	8.7	17.0
		12.7	11.8	11.7
		11.0	....	26.5
		....	....	20.3
		....	....	19.8
		....	....	27.0
		....	....	24.7
Mean		7.7	10.2	21.6

Larger doses of sodium bicarbonate (2 or more grams per kilogram) depress secretion even when unlimited water is allowed (table 2, column 1). The giving of such amounts is often followed by vomiting, and experiments in which this occurred are omitted from the tables.

The Question of a Direct Action of Sodium Bicarbonate by Contact with the Gastric Mucosa.—One dog was trained to lie quietly on the table while the pouch was being irrigated with a solution of sodium bicarbonate. The fluid was delivered at the inner extremity of the pouch through a small bent glass tube, which passed along the lumen of a larger rubber tube. The latter was closed at its inner end, except for a small opening through which the glass tube projected. The solution thus flowed out toward the fistula in contact with the mucosa. Just within the fistula it reentered the large tube, through perforations, and drained out. The inflowing solution was siphoned from a large container in which it was kept at from 37 to 39 C., the temperature never varying beyond those limits. Concentrations of 2.5 and 5 per cent were used. The irrigation was maintained for one hour, about 600 cc. of solution flowing

through in that time. The alkali was finally washed out with 25 cc. of water at 38 C., and the pouch allowed to drain for ten minutes with the dog on its feet. Histamine was then administered and the gastric juice collected for the usual period of two hours.

The last column in Table 2 shows the results. The average figure is slightly greater than that found in the controls, but the difference is perhaps not great enough to be of any significance. There is at any rate no evidence of diminished secretory activity in the pouch.

COMMENT

Most of the numerous experiments in this field have dealt with the influence of the alkalis on the gastric response to some standard meal. This response varies from day to day under the most constant conditions yet obtained. Failure to take these variations sufficiently into account is probably responsible for most of the conflicting statements regarding the effect of the alkalis. Histamine has not previously been used in the study of this problem, so far as I can learn. Bickel [4] used pilocarpine to stimulate secretion in dogs. He reported that sodium bicarbonate would stop such secretion in progress, and prevent any response to a second administration of pilocarpine. Details as to dosage or number of experiments were not given, so it is not possible to compare his observations with those here presented. The results given in this paper with those of my earlier papers, indicate that as a means of reducing gastric secretion moderate doses of sodium bicarbonate are ineffective unless water is withheld. The amount, up to about 1 Gm. per kilogram of body weight, seems to be of less importance than the concentration. Doses above this range may depress secretion or even stop completely the formation of acid. Such massive doses, however, may produce some rather unpleasant symptoms in human subjects.[5]

The control experiments may be criticized on the ground that no water was allowed for twelve hours before the histamine was administered, while 200 cc. or more of water was given with each feeding of alkali. The effect of water as a gastric stimulant is well known. It augments the secretory response to food [6] and would doubtless increase the average volume of juice secreted following histamine. A 2.5 per

4. Bickel, A.: Experimentelle Untersuchungen über den Einfluss von Alkalien und Säuren auf die sekretorische Funktion der Magenschleimhaut, Berl. klin. Wchnschr. **42**:869, 1905.

5. Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, Arch. Int. Med. **31**:171 (Feb. 15) 1923. Kast, Ludwig, Myers, V. C., and Schmitz, H. W.: Clinical Conditions of Alkalosis, J. A. M. A. **82**:1858 (June 7) 1924.

6. Ivy, A. C.: Contributions to the Physiology of the Stomach. XLVIII. Studies in Water Drinking, Am. J. Physiol. **46**:420 (July) 1918.

cent solution of bicarbonate has no such effect if given before histamine, and I have elsewhere reported [1] that a 2.5 per cent solution of sodium bicarbonate, given on the empty stomach, is a much less effective stimulant of gastric secretion than is an equal volume of water. Sodium bicarbonate in such concentrations may then be said to prevent the water in which it is dissolved from acting as a stimulant. Only in this sense can it be said to have a depressing effect.

SUMMARY

1. Sodium bicarbonate given in 2.5 per cent concentration in amounts up to 1 Gm. per kilogram of body weight does not affect the gastric response to a subsequent stimulation by histamine.

2. The same amount of sodium bicarbonate given in 5 per cent concentration reduces the secretion caused by histamine. It is believed that this effect is due mainly to dehydration.

3. Massive doses (2 or more grams per kilogram of body weight) reduce the response to histamine regardless of water allowance.

4. The application of solutions of sodium bicarbonate (2.5 and 5 per cent) to the gastric mucosa for one hour periods does not affect the response of the mucosa so treated to subsequent stimulation by histamine.[7]

7. The histamine dihydrochloride used was supplied through the courtesy of Dr. M. T. Hanke, of the Otho S. A. Sprague Memorial Institute of the University of Chicago.

I wish also to thank Mr. Byford F. Heskett for assistance in some of the experimental work.

THE AUSCULTATORY GAP IN SPHYGMOMANOMETRY

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The clinical importance and the finding of only a rare reference in the English language to the auscultatory gap in sphygmomanometry indicate the need of a detailed presentation of the subject. For this purpose we have studied thirty cases.

The auscultatory gap, "le trou auscultatoire" of the French, is that interval of absolute or relative silence occasionally found on listening over an artery during deflation of the blood pressure cuff; it usually begins at a variable point below the systolic pressure and continues for from 10 to 50 mm. of mercury.

LITERATURE

In 1917, Cook and Taussig [1] reported a period of complete silence during the second phase of determination of blood pressure by the auscultatory method. They estimated that this phenomenon occurred in 5 per cent of hypertensive cases. In 1918, Tixier [1a] noted a short zone of silence below the systolic pressure.

In 1919, Gallavardin and Tixier [2] recorded one case of auscultatory gap and in the following year Poulain [3] added reports of six others. All of these cases, however, were associated with aortic stenosis.

In 1920, Etienne and Richard,[4] and Lian [5] discussed the occurrence of the auscultatory gap in conditions other than aortic stenosis, chiefly in cases of hypertension.

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1. Cook, J. E., and Taussig, A. E.: Auscultatory Blood Pressure Determination; A Source of Possible Error, J. A. M. A. **68**:1088 (April 14) 1917.

1a. Tixier, L.: La méthode auscultatoire en sphygmomanométrie, Paris méd. **27**:449, 1918.

2. Gallavardin, L., and Tixier, L.: Dissociation sphygmomanométrique oscillatoire et vibro-auscultatoire dans un cas de rétrécissement aortique serré et insuffisance aortique avec pulsus tardus et anacrotisme, Arch. d. mal du coeur **12**:447, 1919.

3. Poulain, P.: Deux signes sphygmomanométriques du rétrécissement aortique; trou auscultatoire et labilité tensionnelle systolique, Thèse Lyon, 1920.

4. Étienne, G., and Richard, G.: A propos de deux cas de dissociation sphygmomanométrique, Rev. méd. de l'est **48**:460, 1920.

5. Lian, C.: Etude critique des méthodes sphygmomanométriques et présentation d'un phono-sphygmomètre, Bull. et mém. Soc. méd. d. hôp de Paris **44**: 1643, 1920.

In 1920, Gallavardin and Tixier [6] and in 1921, Gallavardin and Barbier [7] reported that the auscultatory hole was found occasionally in patients exhibiting aneurysm or compression of the subclavian or brachial artery, and that it was not infrequently observed in marked hypertension.

In 1921, Molle [8] described a silent area in or near the center of the pulse pressure, and reported five cases in which the auscultatory gap was unilateral.

In 1926, two English authors, Dally [9] and Heatherly,[10] mentioned the auscultatory gap in their books on cardiovascular disease but did not describe it in detail.

It will be recalled that in 1905 Korotkoff [11] suggested the value of auscultation in the determination of blood pressure. He called attention to the fact that while the pressure in the cuff was gradually reduced from above the systolic value, a succession of sounds could be heard over the artery distal to the cuff. He originally distinguished four phases of sound; subsequently, one phase was divided, so that five phases are now differentiated, as shown diagrammatically in figure 1. The initial phase, characterized by sharp sounds, is apparently due to the sudden distention of the collapsed artery caused by the return of the pulse wave. The beginning of this phase indicates the systolic pressure. In the second phase, a murmur is superimposed on the sound, probably due to whorles or eddies in the blood current as it traverses the arterial constriction and drops to a lower pressure on entering the uncompressed portion of the artery below the cuff. In the third phase, the murmur disappears and the sounds become louder and more intense, due probably to sudden vibrations of the vascular wall produced by an increased volume of blood flow. After reaching a maximum, these sounds abruptly lose their special character. The beginning of the fourth phase is the auscultatory index of the diastolic pressure. The sounds during this phase are muffled, dulled and inconstant, and sometimes are barely audible. At this time the external pressure is probably insufficient to cause distortion of the artery, the latter remaining filled

6. Gallavardin, L., and Tixier, L.: La méthode auscultatoire moyen d'étude du mode de réplétion artérielle; trous auscultatoires, Paris méd. **37**:25, 1920.

7. Gallavardin, L., and Barbier, J.: Le trou auscultatoire et ses conditions de production, Lyon méd. **130**:605, 1921. Barbier, J.: Pathogénie de la zone des souffles de la courbe auscultatoire, Arch. d. mal. du coeur **14**:541, 1921.

8. Molle, M.: Le trou auscultatoire, Bull. méd. Paris **35**:925, 1921.

9. Dally, H.: High Blood Pressure, Its Valuation and Control, New York, William Wood & Co., 1926.

10. Heatherly, F.: Modern Methods in the Diagnosis and Treatment of Heart Disease, New York, William Wood & Co., 1926.

11. Korotkoff, N. S.: Tr. Imp. Mil. Med. Acad. St. Petersburg, **11**:542, 1905.

during diastole. The fifth phase of silence follows. Although this series of sounds is usually heard when there is good functional equilibrium between the heart and arteries, there are frequently individual variations.

TYPES OF AUSCULTATORY GAP

There are three types of gap in auscultatory sphygmomanometry. The first, the complete gap, appears to be the most common, and presents a zone of absolute silence in the auscultatory curve between two sonorous points. The second, the incomplete gap, is not infrequently observed, and is represented by a zone of marked diminution in the intensity of the normal sounds or murmurs. In the third, the variable type of gap,

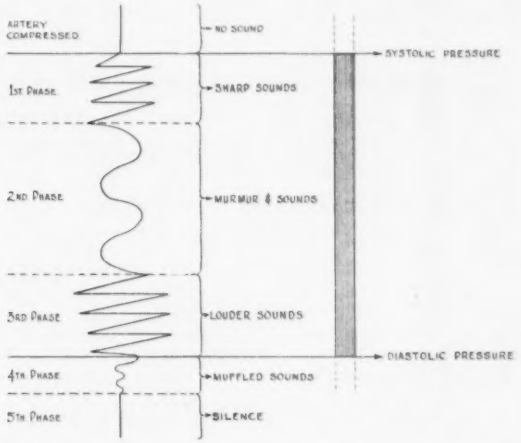

Fig. 1.—Diagrammatic representation of the five sound phases in auscultatory sphygmomanometry.

there is no fixed hiatus in the auscultatory curve, but an inconstant diminution of the sounds may occur, dependent on changing conditions of the pulse, ventricular contraction or tonicity of the arteries. The differentiation between the three types is not always definite.

The silent zone is most frequently observed in the second, or murmur, phase; however, it may be found nearer the upper or the lower limit of the pulse pressure. Occasionally, when the auscultatory hole occurs near the maximal arterial pressure, there may be a so-called dissociation between the auscultatory and palpatory method in sphygmomanometry indicating, as shown in one of our cases, a systolic pressure of 200 mm. by the palpatory method and a maximal pressure of 180 mm. by the auscultatory method. The gap rarely occurs near the diastolic end of the auscultatory curve.

PRESENT SERIES OF CASES

In our series of thirty cases, as shown in figure 2, the average systolic blood pressure was 205 mm., with a range of from 140 to 280. The average disastolic pressure was 97 mm., the variation being from 20 to 150. The average pulse pressure was 108 mm., with a range of from 65 to 160. The average upper limit of the auscultatory gap was 177 mm., the variation being from 110 to 200. The average lower limit of the gap was 150 mm., with a range of from 90 to 190. The

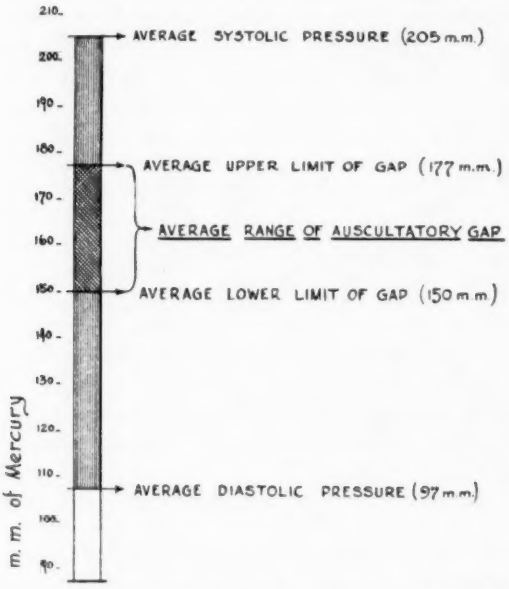

Fig. 2.—Average systolic and diastolic pressure in a series of thirty cases, showing the average range and position of the auscultatory gap.

average extent of the auscultatory hole was 27 mm.; the smallest gap was 10 and the largest 50

In 18 (60 per cent) of our thirty cases, the gap occurred in the upper third of the pulse pressure; in eleven cases (37 per cent), the silent zone was found in the middle third, and in one case (3 per cent), in the lower third of the pulse pressure.

In our series the auscultatory gap was complete in twenty-six cases (87 per cent) and incomplete in four cases (13 per cent). The latter type occurred in patients who had evident hypertension in each instance. There was occasional variability between the two arms, the gap being

more easily demonstrated on one side. Observations on the same patient during repeated visits showed inconstant variations in the presence and position of the gap in several instances.

The auscultatory gap is of considerable clinical importance because of the error that may be occasioned by disregarding the possibility of its occurrence. The most frequent mistake is in the determination of the systolic pressure. If while taking the blood pressure of a person in whom an auscultatory gap is present the pressure is not carried above the gap, the systolic tension may be observed to be far lower than its actual value, since the unwary observer may falsely interpret the lower limit of the gap as the systolic pressure. On the other hand, if the cuff is inflated to a pressure high enough to obtain the correct systolic tension, the beginning of the upper limit of the gap may be mistaken for the diastolic pressure.

Classification of Diagnoses in Thirty Cases Exhibiting Auscultatory Gap

Diagnosis	No. Cases	Per Cent
Hypertensive and arteriosclerotic heart disease (two cases of complete heart block are included)	13	43
Essential hypertension with cardiac enlargement without evident arteriosclerosis	7	23
Rheumatic and hypertensive heart disease (two cases of aortic stenosis are included)	5	17
Essential hypertension without evident cardiac enlargement or arteriosclerosis	2	7
Rheumatic heart disease, with aortic stenosis	2	7
Syphilitic and hypertensive heart disease	1	3
Hypertension (total cases)	28 (93%)	
Aortic stenosis (rheumatic, total cases)	4 (13%)	

The auscultatory hole is not demonstrable in the oscillometric method or by palpation of the radial pulse, and therefore these are valuable checks to prevent error occasioned by the occurrence of the gap.

In our group of thirty cases, as shown in the table, a diagnosis of hypertensive and arteriosclerotic heart disease was made in thirteen (43 per cent). Two cases of complete heart block are included in this group. In one of these, myxedema and syphilis were also present. (This is the only case in which autopsy was performed, and in this instance the clinical diagnosis was confirmed). Essential hypertension with cardiac enlargement but without evident arteriosclerosis occurred in seven cases (23 per cent). Rheumatic and hypertensive heart disease was present in five cases (17 per cent), and of these, two showed aortic stenosis. Essential hypertension without evident cardiac enlargement or arteriosclerosis was diagnosed in two cases (7 per cent). Rheumatic heart disease with definite aortic stenosis was also found in two cases (7 per cent). Syphilitic and hypertensive

heart disease was present in one case (3 per cent). Thus, hypertension was evident in a total of twenty-eight cases (93 per cent), three of which were associated with chronic nephritis. Aortic stenosis on a rheumatic basis occurred in a total of four cases (13 per cent), three of which showed evidence of aortic regurgitation. Thus hypertension, aortic stenosis, or both, occurred in every case.

In our series, thirteen (43 per cent) of the patients were men and seventeen (57 per cent) women. The average age was 56, the youngest patient being 31 and the oldest 79. The average pulse rate was 78, with a range from 36 to 100.

Variable symptoms were noted; the most important ones were dyspnea on exertion in sixteen cases (63 per cent), palpitation following effort, eleven cases (37 per cent), and angina pectoris and congestive failure, six cases each (20 per cent). The arterial walls were slightly thickened in five cases (17 per cent), and moderately thickened in two cases (7 per cent). Arcus senilis was noted in three patients (10 per cent).

COMMENT

Cook and Taussig,[1] Gallavardin and Barbier,[7] Gallavardin and Tixier[12] and Molle[8] have advanced theories as to the mechanism involved in the production of the auscultatory gap. Five factors are worthy of note: first, a point of constriction in the artery through which the blood passes; second, a decrease in the pressure gradient below the point of constriction as compared with the pressure above; third, the type of pulse wave; fourth, failure of resonance of the arterial wall, and fifth, the peripheral resistance and vascular tone of the artery.

In 1916, Erlanger[13] arranged a compression chamber and a stethoscope on the isolated femoral artery of the dog and demonstrated that the sounds in the first and second phases become faint and often disappear if the artery below the stethoscope is temporarily occluded.

The explanation of the auscultatory hole in hypertensive cases may be related to a type of pulse wave showing slight anacrotism or plateau form, as indicated in figure 3, which represents a brachial pulse tracing of a patient who had essential hypertension, coronary sclerosis and complete heart block, but without a demonstrable aortic lesion. Failure of resonance of the arterial wall may be an additional factor in the hypertensive group. Furthermore, if there is increased peripheral resistance in the hypertensive cases, the blood pressure during the second phase when the flow into the artery distal to the cuff is ordinarily rapid, may

12. Gallavardin and Tixier (footnotes 2 and 6).

13. Erlanger, J.: Studies in Blood Pressure Estimations by Indirect Methods: II. The Mechanism of the Compression Sounds of Korotkoff, Am. J. Physiol. **40**:82, 1916.

mount, owing to the high peripheral resistance, to a height sufficient to cause the sounds to disappear for a definite interval and to become audible again when the louder sounds of the third phase develop.

The gap that occurs in aortic stenosis is probably due to reduced velocity of the pulse wave through the arteries associated with slowly rising or plateau pulses, some of which show anacrotism. Figure 4, a brachial pulse tracing of a patient with rheumatic heart disease, illustrates this point. The valvular lesions in this case were aortic and mitral stenosis and regurgitation. The tracing was made while the

Fig. 3.—Brachial tracing of a patient who had essential hypertension, coronary sclerosis, and complete heart block, but without a demonstrable aortic lesion. The blood pressure was 180, systolic; 90, diastolic. The complete auscultatory gap was from 160 to 130 mm. of mercury. Time interval = 0.2 second, every fifth mark being omitted.

Fig. 4.—Brachial tracing of patient who had aortic and mitral stenosis and regurgitation (rheumatic heart disease) taken while the brachial artery was being decompressed and during auscultatory gap. The blood pressure was 150, systolic; 20, diastolic. The complete gap was from 120 to 90 mm. of mercury. Time interval = 0.2 second, every fifth mark being omitted.

brachial artery was being decompressed and during the auscultatory gap, when the pressure in the blood pressure cuff was 110 mm. of mercury. In the anacrotic pulse there is a rise of arterial pressure at the beginning of ventricular contraction, then a short interval or "dead point," during which the arterial pulse loses its vigor, and subsequently a second rise in arterial pressure until the maximal systolic tension is reached. Reduced velocity of the pulse wave accompanied by a slowly rising pulse may also furnish an explanation for the auscultatory gap when it is dependent on an aneurysm or compression of the subclavian or brachial artery.

SUMMARY

The clinical importance of the auscultatory gap in sphygmomanometry is emphasized because of the error that may be occasioned if the possibility of its occurrence is disregarded.

A review of the literature is presented.

Three types of auscultatory gap are considered: (1) the complete gap, (2) the incomplete gap and (3) the variable type of gap.

Thirty cases are reported and analyzed. Hypertension was evident in twenty-eight patients (93 per cent) and aortic stenosis in four (13 per cent). Every case showed either hypertension, aortic stenosis, or both (2 cases).

Factors referable to the mechanism of the auscultatory hole are discussed.

No definite prognostic significance is attached to the auscultatory gap, the outlook depending on the underlying pathologic condition in each case.

THE EFFECT OF TOXEMIA ON TOLERANCE FOR DEXTROSE *

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The fact that toxemias, from whatever origin, cause a disturbance in the tolerance for dextrose of laboratory animals or human beings has been definitely established. This has been noted clinically and experimentally. Clinically, it is illustrated by the much feared infections of diabetic patients. The effect is that of producing a delay in the removal of dextrose from the blood stream or, in other words, a decreased tolerance. The exact explanation of this phenomenon is lacking. Lawrence and Buckley,[1] judging from a series of experiments on rabbits intoxicated with diphtheria toxin, are of the opinion that it is due to a glycogenolysis produced by a stimulation of the "thyroid adrenal apparatus." Tisdall and his co-workers,[2] experimenting with puppies intoxicated with diphtheria toxin and histamine, do not come to any definite conclusion regarding the explanation of this phenomenon. They feel that intoxication may produce its effect on the tolerance for sugar either by an increase in the glycogenolytic function of the body or by an impairment of the ability of the organism to store carbohydrates.

It occurred to us that a series of tests of the tolerance for dextrose of toxic animals with varying degrees of toxemia might give some information as to what extent their tolerance is disturbed and what the nature of the disturance might be.

Rabbits were used for the experiments. A single injection of diphtheria toxin [3] was given subcutaneously. A suitable dosage was determined to produce a toxemia that would cause the rabbit's death within from five to seven days. This dosage was found to be from 0.01 cc. to 0.0075 cc. of the toxin employed in the tests. All of the animals including the controls were starved during the experiments, in order to eliminate the effects of diet and to keep uniform the effect of the starva-

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* From the Departments of Internal Medicine and Physiology, Baylor University College of Medicine.

1. Lawrence, R. D., and Buckley, O. B.: Brit. J. Exper. Path. **8**:1 (Feb.) 1927.

2. Tisdall, Frederick F.; Drake, T. G. H., and Brown, Alan: Production of Lowered Carbohydrate Tolerance in Dogs, Am. J. Dis. Child. **32**:854 (Dec.) 1926.

3. I am indebted to the Eli Lilly Company, who supplied the diphtheria toxin.

tion. (One of us [4] has previously reported the effect of diets on tolerance for dextrose.) On the day preceding the administration of dextrose, all food was removed from the animals' cages. Water was allowed. On the following day, a test of the tolerance for dextrose was made on each animal. Five grams of dextrose in 25 cc. of water was

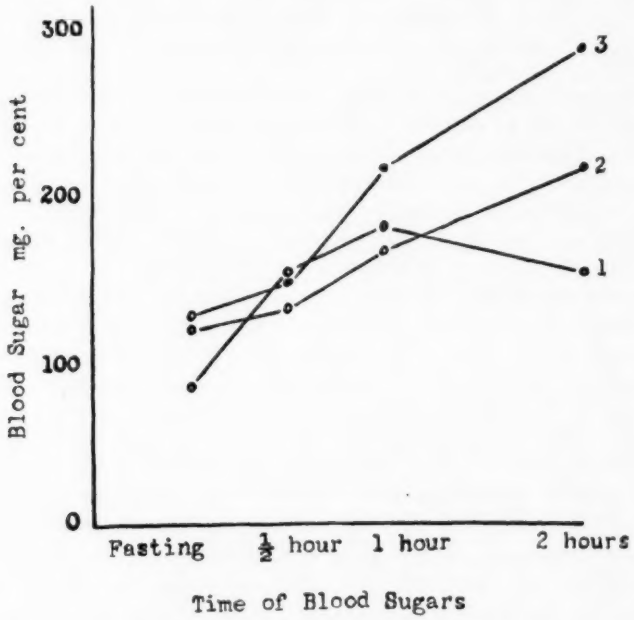

Chart 1.—Daily curves showing the tolerance for dextrose of rabbit 2 following subcutaneous injection of 0.012 cc. of diphtheria toxin (minimum lethal dose equals 0.03 cc.). The numbers at the end of each curve indicate the day of toxemia.

TABLE 1.—*Results of Daily Tests of Tolerance for Dextrose on Rabbit 2 Following Subcutaneous Injection of 0.012 cc. of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 cc.)*

Hours of Starvation	Hours of Toxemia	Temperature (F.) Rectal	Blood Sugar, Mg. per 100 Cc.			
				After Dextrose		
			Fasting	30 Minutes	60 Minutes	120 Minutes
48	24	106.4	89	152	179	152
72	48	102.6	111	129	167	211
96	72	103.5	120	149	211	286

4. Sweeney, J. Shirley: Dietary Factors that Influence the Dextrose Tolerance Test, Arch. Int. Med., to be published.

then given by stomach tube to each rabbit. Samples of blood were drawn from the marginal veins of the ear for determinations of the sugar content before the administration of the dextrose and thirty, sixty and one hundred and twenty minutes following. In this manner, tests of the tolerance for dextrose were run every twenty-four hours until the death of the animals, in order to observe the effect of an increasing

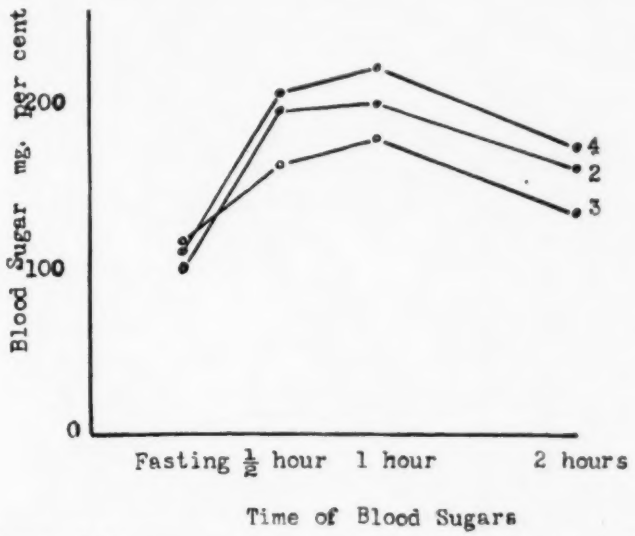

Chart 2.—Daily curves showing the tolerance for dextrose of rabbit 4. Toxin was not given. The numbers at the end of each curve indicate the day of starvation.

toxemia.[5] Control or nontoxic rabbits were treated in the same way. Rectal temperatures were taken daily at the end of each test.

TABLE 2.—*Results of Daily Tests of Tolerance for Dextrose on Rabbit 4, Used as Control for Rabbit 2, Table 1. Did Not Receive Toxin*

Hours of Starvation	Temperature (F.) Rectal	Blood Sugar, Mg. per 100 Cc. Fasting	After Dextrose 30 Minutes	60 Minutes	120 Minutes
48	104	100	196	200	157
72	102.8	111	160	182	136
96*	103.3	107	204	217	174

* Rabbit was fed following this test and was apparently normal the next day.

5. There is some effect of the dextrose on the tests of the tolerance for dextrose performed day after day. This was noted in some control animals not included in this series. This phenomenon is being studied at present.

The results of these tests of tolerance for dextrose are listed in tables 1, 2, 3, 4 and 5 and presented graphically in charts 1, 2, 3, 4 and 5. It will be noted that only three toxic rabbits were used. The effect of the toxemia was so marked and so uniform that additional observations were considered unnecessary.

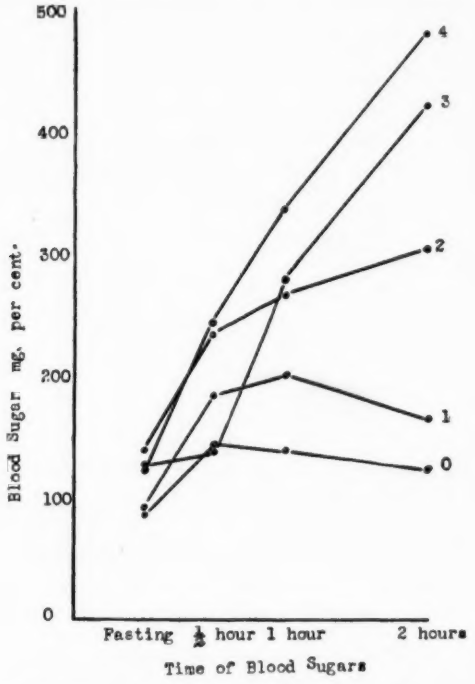

Chart 3.—Daily curves showing the tolerance for dextrose of rabbit 8 following subcutaneous injection of 0.01 cc. of diphtheria toxin (minimum lethal dose equals 0.03 cc.). The numbers at the end of each curve indicate the day of toxemia.

TABLE 3.—*Results of Daily Tests for Tolerance for Dextrose on Rabbit 8 Following Subcutaneous Injection of 0.01 cc. of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 cc.)*

Hours of Starvation	Hours of Toxemia	Temperature (F.) Rectal	Blood Sugar, Mg. per 100 Cc.			
			Fasting	After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
24	..	.....	89	148	143	123
48	24	103.1	93	182	200	160
72	48	101.5	140	217	263	303
96	72	102.1	129	143	278	417
120	96	101	125	241	333	479

The most striking phenomenon to be noted is the positive association between the degree of toxemia (if it may be assumed that there was a daily increasing toxemia in the rabbits) and the impairment of the tolerance for dextrose. In other words, as the rabbits' toxemia became greater, their ability to remove the ingested dextrose from the blood stream became less. In no instance was there a suggestion of improved tolerance during the course of the toxemia. This would suggest that

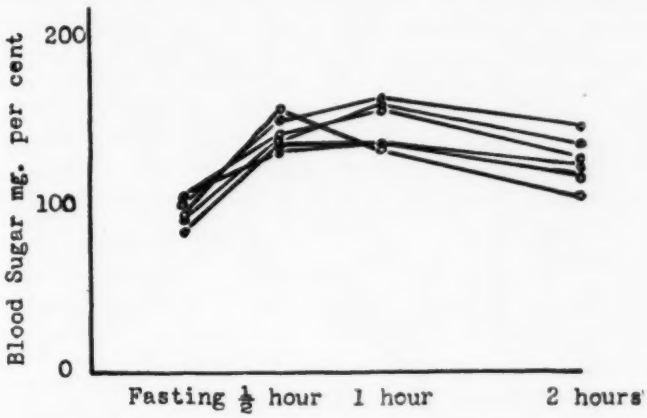

Chart 4.—Daily curves showing the tolerance for dextrose of rabbit 5. Toxin was not given. The figures are given in table 4.

TABLE 4.—*Results of Daily Tests for Tolerance for Dextrose on Rabbit 5, Used as Control for Rabbits 8 and 7, Tables 3 and 5. Did not Receive Toxin.*

Hours of Starvation	Temperature (F.) Rectal	Blood Sugar, Mg. per 100 Cc.			
			After Dextrose		
		Fasting	30 Minutes	60 Minutes	120 Minutes
24	.....	103	133	138	125
48	103	92	156	133	105
72	103.1	82	135	138	114
96	103	100	150	167	148
120	103	103	143	154	128
144	103.8	95	141	160	132

there might be a quantitative relationship between toxemia and the tolerance for dextrose. Tisdall and his co-workers [2] did not make daily tolerance tests on their toxic animals. The degree of postprandial hyperglycemia of their animals from twenty-four to seventy-two hours following the injection of diphtheria toxin is in accord with the results presented in this study. There is apparently no uniform relationship

between temperature and tolerance for dextrose. If any such relationship exists, it appears to be that the tolerance is less when the temperature is at a lower level. It will be noted from the tables that this was true in a number of instances. Lawrence [1] noted this apparent relationship of temperature and the level of blood sugar in his studies.

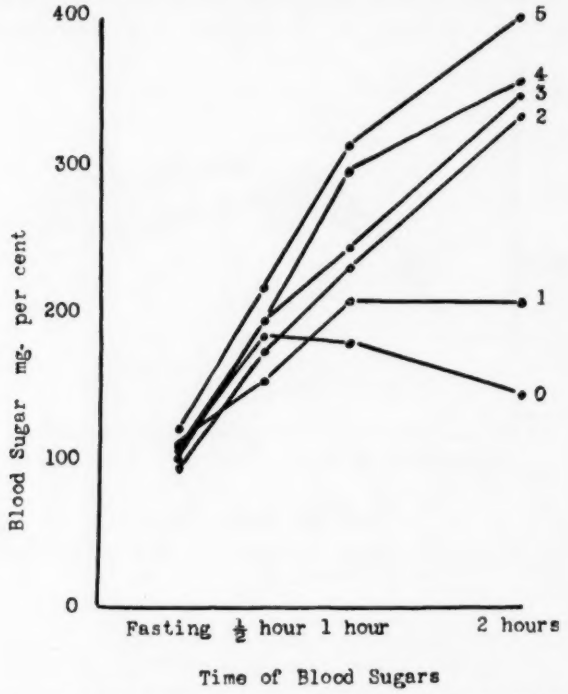

Chart 5.—Daily curves showing the tolerance for dextrose of rabbit 7 following subcutaneous injection of 0.0075 cc. of diphtheria toxin (minimum lethal dose equals 0.03 cc.). The numbers at the end of each curve indicate the day of toxemia.

TABLE 5.—*Results of Daily Tests of Tolerance for Dextrose on Rabbit 7, Following Subcutaneous Injection of 0.0075 cc. of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 cc.)*

Hours of Starvation	Hours of Toxemia	Temperature (F.) Rectal	Blood Sugar, Mg. per 100 Cc.			
				After Dextrose		
			Fasting	30 Minutes	60 Minutes	120 Minutes
24	..	.....	105	182	179	145
48	24	104.6	107	152	206	206
72	48	101.8	95	174	220	333
96	72	101.2	100	190	244	345
120	96	102.7	109	190	296	357
144	120	102.6	120	215	313	400

There is another interesting observation that is noteworthy in these studies, and that is that marked toxemias have little, if any, effect on the absorption of the orally administered dextrose. In one instance an animal died within a few hours after the test of its tolerance for dextrose had been finished and his two hour postprandial level of blood sugar was 400 mg. per hundred cubic centimeters of blood. We believe that it may be concluded from this evidence that toxemias do not seriously interfere with the gastro-intestinal absorption of dextrose. One other observation is that toxemias cause a higher level of the blood sugar after fasting. This effect has been noted by many observers.

This phenomenon of the animals' increasing inability to remove the dextrose from the blood stream is probably to be explained in one of four ways: (*a*) by an increase in the glycogenolytic function of the body, (*b*) by an impairment of the glycogenic function, (*c*) by a suppression of the oxidative function and (*d*) by either a disturbance in the action or in the production of insulin, either of which is inextricably associated with one or all of the foregoing possibilities. Until the action of insulin is definitely determined, it must of necessity be difficult to explain these phenomena. We believe [4] that the action of insulin is principally that of glycogenesis. If this be true, the most probable explanation of a decreased tolerance in the presence of a toxemia is some disturbance in the production or action of insulin. Experiments are now being completed that we believe will add weight to this hypothesis.

SUMMARY AND CONCLUSIONS

Rabbits made toxic by diphtheria toxin are shown to have a marked decrease in tolerance for dextrose. The decrease in tolerance becomes more marked during the course of the toxemia. This suggests a quantitative relationship between toxemia and tolerance for dextrose. It is suggested that the explanation of this phenomenon lies in a disturbance of insulin action or insulin production.

The toxemia did not have a noticeable effect on gastro-intestinal absorption of the dextrose.

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HYPERTENSIVE ENCEPHALOPATHY *

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In the course of acute glomerulonephritis and less commonly in other varieties of chronic interstitial nephritis, there may occur acute episodes of cerebral phenomena, such as epileptiform convulsions, coma, headache, amaurosis, hemiplegia and aphasia. In the past, these episodes were generally included under the concept of uremia and were termed acute uremia. Since the beginning of the present century, convincing evidence that these cerebral episodes are not uremic in nature has gradually accumulated. This evidence will be summarized later in the paper. It has become clear that these cerebral symptoms are correlated with hypertension, being a manifestation of circulatory disturbances in the brain consequent on the hypertension. For this reason, we have termed the cerebral syndrome the hypertensive encephalopathy. The nature of the hypertensive encephalopathy is well illustrated in the following case. We have had the patient under continuous observation over a period of twenty months at the Mount Sinai and Montefiore Hospitals.

REPORT OF A CASE

History.—S. S., a college student, aged 19, entered Mount Sinai Hospital, Sept. 7, 1925, in an aphasic state following a convulsion four hours before entrance.

He had pneumonia when 8 years old. His tonsils were removed when he was 12. From then to January, 1925, he was perfectly well.

In January, he became ill with bronchopneumonia, and was confined to his bed for six weeks. Following his recovery, he again became sick, this time with acute rheumatic fever. Painful, swollen joints, fever and cardiac involvement, as evidenced by a diastolic murmur, were present. At this time, the patient's systolic blood pressure was 120 mm., and the urine did not contain any albumin. He seemed to have completely recovered by May 20; the blood pressure was normal and the urine free from albumin. About Aug. 1, 1925, he began to suffer from frontal headaches which prevented him from sleeping. At this time, his family physician found that he had arterial hypertension and that his urine contained albumin and blood. The headaches became progressively worse, and to them were added attacks of vomiting. On September 7, following a period of restlessness, he had a severe convulsion. Four hours after the convulsion he was brought to the hospital, aphasic but conscious.

On admission, the patient was drowsy and apathetic. He was able to respond to questions only by repeating words used by the questioner. The pupils were equal and regular, the action of the left being the livelier. The heart was

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* From the medical divisions of Mount Sinai and Montefiore Hospitals.

* Read in abstract before the Association of American Physicians, Atlantic City, New Jersey, May 3, 1927.

somewhat enlarged to the left, the forceful apex beat being felt in the fifth interspace outside the midclavicular line. The first sound at the apex was booming and was followed by a short systolic murmur. The second sound, at the aortic area, was greatly accentuated and clanging. The radials felt thickened and hard. The blood pressure was 200 mm. systolic and 110 mm. diastolic. The right knee reflex was livelier than the left; no Babinski sign or other pathologic reflexes were present. The urine had a specific gravity of 1.022, and contained a faint trace of albumin and a few granular casts. Examination of the blood showed: hemoglobin, 106 per cent; red blood cells, 6,600,000; white blood cells, 28,000; polymorphonuclears, 88 per cent; lymphocytes, 6 per cent, and monocytes, 4 per cent. The Wassermann reaction was negative, and the blood culture proved sterile. The blood chemistry was: nonprotein nitrogen, 31.4; urea nitrogen, 14.0; uric acid, 4.2; creatinine, 1.2 mg. per hundred cubic centimeters.

Beginning at 3 a. m. of the night following admission, the patient had several right-sided convulsions. During these convulsions, each of which was of one or two minutes' duration, the head was turned to the right, the eyes rolled upward and to the right, and there were clonic movements of the right side of the face, right arm, trunk, and right lower extremity. Following these, there were generalized bilateral convulsions which were stopped by the administration of a little chloroform. At this time neither plantar nor abdominal reflexes could be elicited. The knee and ankle reflexes were active and equal, without clonus. The left pupil was larger than the right and reacted sluggishly with hippus. A phlebotomy of 400 cc. was carried out and lumbar puncture performed. It revealed the cerebrospinal fluid to be under normal tension, clear, and containing no cells.

The next morning the patient was extremely anxious, restless and inattentive. The left palpebral fissure was narrower than the right. The left pupil was larger than the right. Both pupils reacted sluggishly to light. There was slight facial weakness on the right. The right biceps and triceps reflexes were more active than the left. The knee reflexes were present. A bilateral Babinski sign and a tendency to a right ankle clonus were present.

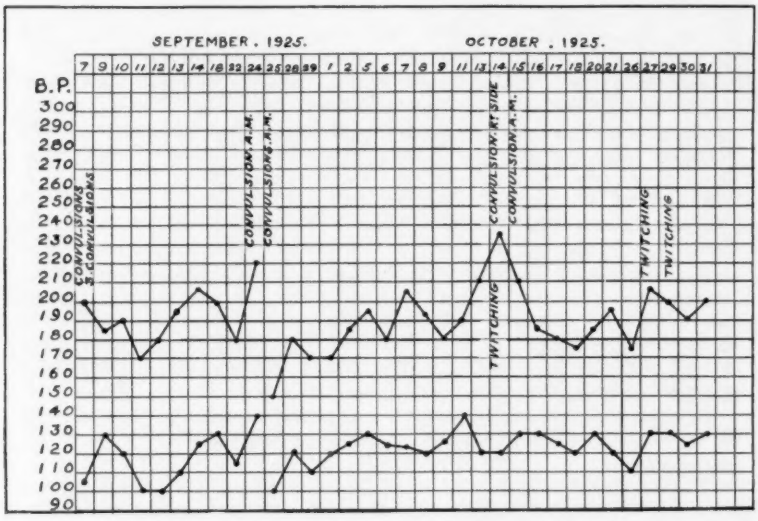
On ophthalmoscopic examination, the arterial blood columns appeared narrow, the vessel wall somewhat thickened. No other abnormalities were noted by the ophthalmologist.

The next day the patient was greatly improved and the Babinski reflexes had disappeared. The blood pressure was 190 systolic and 130 diastolic.

From Sept. 7, 1925, to April, 1927, we have had the patient under continuous observation, first in Mount Sinai and then in Montefiore Hospital and subsequently again at Mount Sinai Hospital. Our observations during this period were as follows:

Neurologic Phenomena.—From the time of his admission to December, 1926, a period of fifteen months, the patient had many convulsive seizures. Sometimes there were several in a day, once more than twenty; at other times a month would pass without one. From April 4, 1926, to Aug. 26, 1926, there were no convulsions. The convulsions were usually preceded by an aura, consisting of headache, a feeling of weakness and paresthesias in the right upper extremity in the form of a tingling in the fingers and "a feeling as though there is no blood in the right arm and hand, and they are paralyzed." From these prodromes, the patient often knew when an attack was imminent. On several occasions, the prodromes were not followed by actual convulsions. The convulsions usually started with tonic and then clonic spasms of the right upper extremity, which then spread to the right lower extremity and finally became generalized. How-

ever, among the later convulsions were some that started with paresthesias of the left upper extremity, which then began to twitch with subsequent involvement of the right side of the body. The convulsions were of varying duration, from a few quick twitches to severe attacks lasting five or more minutes. During the attacks, the patient would foam at the mouth and would appear extremely cyanotic. Consciousness was usually completely lost during the convulsions and for some time thereafter, though during a few mild seizures he remained conscious. On several occasions, the convulsions were quickly aborted by chloroform. The patient did not bite his tongue, but in one nocturnal attack it was necessary for the nurse to separate his clenched teeth with a gag. A few attacks consisted of only transitory pareses of the right upper extremity. Following the attacks, the patient was usually stuporous, but often recovered complete consciousness in a few minutes.



The relation of rises in blood pressure to convulsive seizures.

Between convulsions and immediately after the attack, the pupils reacted slowly to light and sometimes hardly at all; occasionally, anisocoria was present. The tendon reflexes were hyperactive, and the Babinski reflex was present on both sides. The pupillary abnormalities and Babinski reflexes would disappear within a few hours, and between attacks there were no abnormal neurologic manifestations.

Blood Pressure.—At first the blood pressure was about 200 mm. systolic, and 110 mm. diastolic; later it rose to an average of about 230 mm. systolic and 130 mm. diastolic, always being elevated. For several days before most, though not all, of the convulsive seizures, the blood pressure rose markedly, in some cases the rise being as much as 50 mm. each of the systolic and diastolic pressures, as shown in the accompanying chart. After some of the attacks, the pressure fell decidedly, though only temporarily. Thus, in the week prior to the severe convulsive seizure of Sept. 24, 1925, the pressure rose steadily from 170/140 to

220/140 a few hours before the attack, to fall to 150/100 several hours after the attack, the latter being the lowest pressure the patient ever showed.

The pressure of the cerebrospinal fluid was determined on several occasions, the lumbar puncture being carried out either for the relief of convulsive seizures or headache, or to prevent an attack when prodromes were present. The pressure was either normal or only slightly elevated, the highest value being 30 cm. of water.

Kidney function was carefully studied. At no time was there any evidence of serious impairment of renal function. At all times, the patient was able to concentrate the urine to a specific gravity of 1.022 or higher and to dilute normally. There was never any evidence of nitrogen retention, as is shown in the accompanying table.

On Oct. 23, 1925, the plasma chlorides were 540 mg. per cent (as sodium chloride). On Dec. 6, 1926, the calcium content of the serum was 9.7 mg. per cent and on April 5, 1927, 10 mg. per cent.

The urine showed comparatively slight deviations from the normal. Most of the daily examinations revealed a trace of albumin, but this was never heavy, and on many examinations no albuminuria at all was present. Microscopic exami-

Blood Chemical Determinations

Date	Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Creatinine	Cholesterol
9/ 8/25	31.4	14.0	4.2	1.2	...
9/10/25	26.7	14.0	3.0	1.1	...
11/23/25	38.5	15.4	3.5	1.0	...
12/ 2/25	42.1	23.8	6.0	1.4	...
1/11/26	35.0	11.2	3.5	1.1	142
2/ 2/26	28.0	12.6	6.5	1.5	200
3/ 5/26	26.7	11.2	4.0	1.0	...
4/15/26	26.0	11.2	3.5	1.2	...
5/19/26	....	8.8	...	...	164
7/26/26	....	9.7	...	...	...
8/30/26	....	8.4	...	...	...
3/ 2/27	36.9	11.0	2.6	...	...

nation often showed a few hyaline and granular casts, but these were not always present. Red and white blood cells were never found in any considerable quantity, though the history states that the patient had had hematuria at the onset of his illness.

The Retina.—When the patient first entered the hospital, ophthalmoscopic examination revealed only a narrowing of the arterial blood columns and some changes in the arterial walls as evidenced by thin white lines bordering some of the arterial blood columns. Then changes rapidly appeared, so that ten days later, the following symptoms were noted by the ophthalmologist, Dr. Goldstein: "O.D.: the disk is hyperemic. Its margins are fairly distinct, the physiological pit large, and the veins about normal. The tortuous arteries are narrower than normal. To the nasal side of the disk are many irregularly round, grayish white patches about one half the size of the disk; they are situated in the deeper layers of the retina. The macula is very red, surrounded by a prominent light reflex on the temporal side. There are a few exudates on the temporal side. O.S.: the disk is hyperemic with margins somewhat blurred. There is a large physiological cup. The veins are about normal in size, the arteries narrowed. The macula is normal. There are no exudates or hemorrhages."

The typical picture of "albuminuric retinitis" developed quickly, with a stellate figure around the right macula. There were numerous patches of exudate and hemorrhages on both sides. The most striking feature at all times was the

extreme narrowing of the arteries, rendering them difficult to recognize. Papilledema was present at times in slight degree, never becoming marked. The hemorrhages and exudates cleared up entirely during the next eighteen months except for the fine silvery white spots arranged radially around the right macula. The arteries were still narrow in April, 1927.

The patient was at Mount Sinai Hospital in April, 1927. He was ambulatory, though not strong. The vision was somewhat impaired by the albuminuric retinitis, but it was better than formerly and he read without any difficulty. The blood pressure had settled at a constant high level (about 240 systolic; 130 diastolic). No nitrogen retention was present. The last convulsions occurred during March, 1927, and no abnormalities were found on examination of the nervous system.

Summary.—A youth, aged 19, became ill with pneumonia and acute rheumatic fever. Following recovery from these, it was found that the blood pressure was abnormally high and that the urine showed blood and albumin. In the twenty months since then, the blood pressure had remained high, but there had never been any nitrogen retention and in fact no evidence of impairment of renal function had appeared. During this period he had had many epileptiform convulsions from which he quickly recovered. In conjunction with these, he had had transient palsies and on one occasion transient aphasia. On several occasions, it was evident that the convulsive attacks marked the culmination of a period of rising blood pressure, which fell soon after the attack. The pressure of the cerebrospinal fluid was measured on several occasions between or soon after the convulsions, and was either normal or only moderately elevated.

The convulsive seizures in this case illustrate the most striking form of what we term the hypertensive encephalopathy, but generalized epileptiform convulsions are by no means the only way in which the hypertensive encephalopathy may manifest itself. Various other focal and general cerebral symptoms may occur, either in combination with or independent of the convulsions. The convulsions may be unilateral, simulating jacksonian epilepsy. Chauffard [1] described a case in which the unilateral convulsions rapidly alternated from one side to the other. The occurrence of aphasia in such cases has been described by Osler,[2] whose attention was drawn to the existence of such phenomena by the early paper of Peabody.[3] "Uremic" amaurosis is another symptom of the hypertensive encephalopathy which is not extremely rare, the nature of the blindness being disclosed by its association with hypertension, its

1. Chauffard: De l'urémie convulsive à form d'épilepsie jacksonienne, Arch. gén. de méd. **2**:5, 1887.

2. Osler: Transient Attacks of Aphasia and Paralysis in States of High Blood Pressure and Arteriosclerosis, Canad. M. A. J. **1**:919, 1911.

3. Peabody: Relations between Arterial Disease and Visceral Changes, Tr. A. Am. Phys. **6**:170, 1891.

transitory nature, the negative ophthalmoscopic manifestations, apart from possible narrowing of the arteries, and the preservation of the light reflex which shows the cerebral origin. Various motor palsies, cerebral deafness, hemianopia and other focal cerebral symptoms of sudden onset and brief duration are vividly described in the accounts of "acute uremia" of the older authors, though in these descriptions what we here term the hypertensive encephalopathy and symptoms of uremia are indiscriminately mixed. The only symptom that we desire to discuss further here is headache, which is a frequent—we believe the most frequent—manifestation of the hypertensive encephalopathy. Its nature can often be recognized in the absence of other cerebral symptoms when it occurs as the culmination of a rapid rise in blood pressure, is unaccompanied by nitrogen retention and is relieved by venesection or lumbar puncture.

PATHOGENESIS

The postmortem examination of the brain of a patient who presented symptoms of the hypertensive encephalopathy does not reveal any focal lesions to account for the epileptiform convulsions, amaurosis, aphasia or other cerebral manifestations that were so striking during life. The brain is pale, usually almost bloodless. In some instances, the brain substance and meninges are edematous, but in others they do not show any evidence of edema and, in fact, may be unusually dry. In view of this paucity or absence of anatomic changes, it seems necessary to seek the pathogenesis of the hypertensive encephalopathy along "functional" lines. In this connection, two considerations are of paramount importance, namely, the relation of the hypertensive encephalopathy to disturbances of real function and to arterial hypertension.

Renal Function.—It has been known since the time of Christison [4] that epileptiform convulsions and the other features of the hypertensive encephalopathy may occur in chronic interstitial nephritis without any diminution in the volume of urine, though in the majority of cases the seizures do occur during a period of oliguria. It is to Volhard [5] that we are indebted for first demonstrating convincingly that what is here termed the hypertensive encephalopathy is not a consequence of impaired renal function. The application of modern methods of testing renal function (concentration test, dye excretion, etc.) shows that many patients presenting the typical hypertensive encephalopathy have no demonstrable impairment of renal function. Moreover, the blood chemistry is usually normal in all respects. Of course, the underlying kidney

4. Christison: On Granular Degeneration of the Kidneys, Edinburgh, 1839, p. 176.

5. Volhard, in Mohr and Staehelin's Handbuch der inneren Medizin, Berlin, **3**:1346, 1918.

disease may cause a coincident impairment of renal function with its attendant changes in the blood chemistry, but the frequent occurrence of the hypertensive encephalopathy without renal insufficiency shows that there is no obligate connection between the two phenomena. On the other hand, the extreme rarity of symptoms of the hypertensive encephalopathy in the most typical impairment of renal excretion, that due to mechanical obstruction of the urinary passages, shows that retention of urinary constituents is not the cause of the hypertensive encephalopathy.

Similarly inadequate is the hypothesis of Widal,[6] still widely held in France. He believed that the symptoms which we group together as the hypertensive encephalopathy are the results of chloride retention with consequent saturation of the nervous centers with chlorides, and terms them chloruremia. In most cases there is no evidence whatever of chloride retention, and in mechanical urinary obstruction in which enormous chloride retention may occur (the plasma sodium chloride in one case was more than 1,100 mg. per hundred cubic centimeters) without any manifestations of the hypertensive encephalopathy.

It is to be emphasized that severe generalized convulsions, which are the most striking feature of the hypertensive encephalopathy, are rare in true uremia. In fifty-one consecutive cases of chronic interstitial nephritis with renal insufficiency and nitrogen retention, studied at the Mount Sinai Hospital, only two showed generalized convulsions, and in neither of these were they of the extreme severity seen in the hypertensive encephalopathy. In well marked true uremia, slight convulsive movements and particularly fibrillary twitchings are common, apparently being due to the lowered calcium content of the blood that follows on phosphate retention. However, these differ markedly from the generalized convulsions of the hypertensive encephalopathy, which are obviously of cerebral origin.

These considerations indicate that the term "acute uremia" is a misnomer when applied to the acute cerebral episode which we here call the hypertensive encephalopathy. The term acute uremia should be reserved for cases of true uremia of unusually abrupt onset, and it is important from a diagnostic, therapeutic and particularly from a prognostic standpoint to differentiate sharply between true uremia and hypertensive encephalopathy.

HYPERTENSION

The symptoms which are here grouped together as the hypertensive encephalopathy occur in the presence of arterial hypertension. In most cases, this increase of blood pressure is manifest and, in fact, is usually

6. Widal and Lemierre: Die diatätische Behandlung der Nierenentzundingen, Ergebn. d. inn. Med. u. Kinderh. **4**:543, 1909.

extreme. We have seen cases in children in which the existence of arterial hypertension was not immediately manifest, only subsequent observation proving such figures as 120/80 to be above the normal for the child. Moreover, in the presence of cardiac failure, the hypertension may not be manifest, though the peripheral conditions (vasoconstriction) for hypertension are present; we have seen a case of eclamptic convulsions with fatal outcome in which there was other evidence that cardiac insufficiency was the cause of the relatively low blood pressure.

The onset of the cerebral symptoms is often preceded by an additional rise above the already elevated level of blood pressure. This may occur quickly, particularly in eclampsia gravidarum or more gradually over a period of several days, as was evident several times in the case described. After the attack, there is usually a sharp drop in the blood pressure. Both these points are well illustrated in the accompanying chart. The premonitory rise in blood pressure usually affects both systolic and diastolic pressure. Sometimes the rise in the diastolic pressure is disproportionately great, perhaps indicating that the heart is unable to cope fully with the great increase in peripheral resistance.

The fact that a marked rise in blood pressure so often precedes the attack and that the cerebral phenomena often clearly form the culmination of the rise indicates clearly the intimate and probably causal relation of the rise in pressure to the cerebral syndrome.

The causal relation of the hypertension to the hypertensive encephalopathy is further indicated by certain facts concerning the occurrence of the identical cerebral syndrome in the three widely differing conditions of diffuse glomerulonephritis, toxemia of pregnancy and acute lead poisoning, facts which have long been known individually, but whose great importance for the pathogenesis of the cerebral syndrome has been emphasized only in recent years by Vaquez,[7] Pal [8] and Volhard.[9]

In the toxemia of pregnancy, the eclamptic seizure invariably occurs in the presence of arterial hypertension (Vaquez and Nobécourt).[10] The classic form of the eclamptic attack consists in epileptiform seizures in every way analogous to those occurring in glomerulonephritis. The attacks can often be shown to follow an added rise in the blood pressure and to be followed by a drop. As in glomerulonephritis, transitory amaurosis, aphasia, hemiplegia or other focal cerebral symptoms may be part of the syndrome. These may occur in the presence of intact renal

7. Vaquez: Maladies du Coeur, Paris, 1921, p. 477.

8. Pal: Gefässkrisen, Leipzig, 1905.

9. Volhard: Der arterielle Hochdruck, Verhandl, d. deutsch. Gesellsch. f. inn. Med. **35**:134, 1923.

10. Vaquez and Nobécourt: De la pression artérielle dans l'éclampsie puerpérale, Bull. et mém. Soc. méd. d. hôp. de Paris **14**:117, 1897.

function. At necropsy, cerebral anemia and often cerebral edema may be present, as has been demonstrated both post mortem and intra vitam (by trephining) by the exhaustive investigations of Zangemeister.[11]

Lead encephalopathy is also always associated with arterial hypertension (Traube [12] Vaquez [13]). The convulsions are likewise epileptiform in character and may be similarly accompanied by transitory focal cerebral symptoms such as aphasia and amaurosis. Renal function is often entirely intact, though there is usually oliguria during the attack. The anatomic manifestations in the brain are the same as those in the other two conditions, consisting of anemia and sometimes edema (Tanquerel des Planches).[14]

From this brief survey it is seen that the same group of transitory cerebral symptoms may occur in the three etiologically diverse conditions of diffuse glomerulonephritis, acute lead poisoning and the toxemia of pregnancy. The cerebral syndrome cannot be due to renal failure in these conditions for in each of them the symptoms may occur in the presence of entirely intact renal function. Each of the conditions is frequently marked by the occurrence of arterial hypertension, and it is only in the presence of hypertension that the cerebral symptoms present themselves. It is therefore probable that the hypertension is causally connected with the cerebral syndrome. What is the nature of the link between the hypertension and the cerebral syndrome? Two factors, cerebral vasoconstriction and cerebral edema, must be considered in this connection.

Cerebral Vasoconstriction.—All available evidence indicates that, whatever the ultimate causation may be, the immediate mechanism of arterial hypertension in glomerulonephritis is a widespread, and perhaps universal, peripheral vasoconstriction. We have no precise information as to the extent to which individual vascular territories, and particularly those of the brain, are involved in the vasoconstriction. But it has already been mentioned that at the autopsy of patients who had the symptoms of the hypertensive encephalopathy, the brain is usually found pale and the vessels devoid of blood, indicating that the vasoconstriction within the skull has been particularly marked.

Other indirect evidence of vasoconstriction in the brain is sometimes furnished by opthalmoscopic examination, for the retina ("the mirror of the brain") is an embryologic outgrowth of the brain and their blood supplies are closely interrelated. Here it is usually possible to observe

11. Zangemeister: Die Eklampsie eine Hirndruckfrage, Ztschr. f. Geburtsh. u. Gynak. **79**:124, 1916.

12. Traube: Gesammelte Beitrage zur Pathologie und Physiologie **2**:551, 1871.

13. Vaquez: La tension artérielle dans le saturnisme aigu et chronique, Semaine méd. **23**:385, 1904.

14. Tanquerel des Planches: Traité des maladies de plomb, Paris **2**:350, 1839.

in patients with hypertensive encephalopathy that the retinal arteries are narrow; this was repeatedly noted in the case reported, before the actual albuminuric retinitis appeared. There are a number of observations on record in which blindness in acute hypertensive states has been shown by ophthalmoscopic observation to be the result of spastic closure of the retinal arteries, vision returning as the blood flow through these vessels was restored. Among those who have made such observations are Elschnig,[15] Wagenmann [16] and Smith.[17] Labadie-Lagrave and Laubry [18] observed a patient with acute lead poisoning who became almost completely blind when the blood pressure reached 250 mm. of mercury. Vision returned when the blood pressure was lowered to 170 mm. by the administration of amyl nitrite. An hour later the amaurosis recurred, to disappear as the blood pressure gradually fell to normal on the following day.

The most important evidence of the fundamental rôle played by angiospastic phenomena in the genesis of the hypertensive encephalopathy is furnished by the extreme suddenness with which the individual cerebral phenomena come and go, leaving no trace whatever behind them. Moreover, in the same case the focal cerebral symptoms often change. In the case described, the patient had aphasia with the first attack; then his convulsions began on the right side, and later they started on the left side. Sometimes they would affect only the face or an upper extremity, or there would be unilateral convulsions. Chauffard [1] saw a patient in whom the convulsions alternated many times during a day from one half of the body to the other. We are unable to explain such phenomena other than on a vasomotor basis.

Localized vascular spasms may occur in hypertensive patients in parts of the body other than the brain. The observations on the retina have already been mentioned. Not uncommon in hypertensive patients, though actually observed infrequently, is the so-called "phenomenon of the dead finger," first described by Dieulafoy [19] as an initial symptom of uremia. Actually, the dead finger symptom has no relation to uremia but occurs in hypertensive patients whatever the state of renal function. It consists of a sudden feeling in one or more fingers or toes as though they were "dead." The patients may also note that the finger appears

15. Elschnig: Sehstörungen durch Bleivergiftung, Wien. med. Wchnschr. **48**:1305, 1898.

16. Wagenmann: Beitrag zur Kenntnis der Zirkulationsstörungen in den Netzhautgefässen, Arch. f. Ophth. **43**:219, 1897.

17. Smith: Intermittent Closure of Cerebral Arteries, Brit. M. J. **2**:1380, 1909.

18. Labadie-Lagrave and Laubry: Accident aigu du saturnisme et hypertension, Tribune méd. **38**:437, 1906.

19. Dieulafoy: Text Book of Medicine, Translated by Collins and Liebmann, ed. 2, New York, 1912, p. 1112.

white. The "dead" finger symptom passes away as quickly as it came, and even observant patients will usually tell about this phenomena only when questioned specifically. Volhard [9] believed that there is a strong element of cutaneous vasoconstriction in the production of the extreme pallor of many patients, which is out of all proportion to the anemia and in the absence of edema. Lead colic appears only in the presence of arterial hypertension, and Vaquez [7] adduced strong evidence that it is an ischemic pain due to vasoconstriction of the mesenteric vessels.

Cerebral Edema.—The theory that edema of the brain plays a part in the causation of "uremic" attacks was suggested by Owen Rees [20] and elaborated by Traube,[12] who believed the cerebral edema to result from the concommitance of arterial hypertension, which he recognized as always present in "uremia" and hydremia. As a result of the combination of increased blood pressure and hydremia, fluid is pressed through the capillary walls. Since the pressure in the aortic system is higher than that in the capillaries, these are compressed with resultant cerebral anemia, the consequences of which are the convulsions, coma and other cerebral symptoms. Traube's theory was discarded for a long time after Cohnheim [21] showed that edema of the brain is most often absent in uremia, but has been resuscitated by Volhard [9] for certain cases of what we here term the hypertensive encephalopathy. In this country, strong evidence of the significance of edema of the brain for the causation of cerebral attacks in glomerulonephritis has recently been published by Blackfan.[22] Blackfan recognized clearly the nonuremic nature of the cerebral symptom which he believed due to edema of the brain, and suggested that they be termed the cerebral symptoms of acute glomerulonephritis.

Edema of the brain is found in some but not in all patients who have had the symptoms of the hypertensive encephalopathy. The edema may be so marked that on opening the calvarium the dura is found tensely stretched. The convolutions are flattened and the sulci shallow. There may be a conical deformation of the brain stem ("medullary cone"), showing that it has been pressed into the foramen magnum; this is well seen in an illustration by Blackfan. The edema of the brain substance sometimes results in great narrowing of the ventricles (Tanquerel des Planches [14]), so that the latter appear as mere slits when the brain is hardened in situ (Volhard [5]). In other cases, the brain may be dry, as we have seen several times. Such "dry" brains may be found despite

20. Rees: On the Nature and Treatment of Diseases of the Kidney, London, 1850, p. 67; quoted by Senator, Krankheiten der Niere, Vienna, 1902, p. 96.

21. Cohnheim: Vorlesungen über allgemeine Pathologie, Berlin, **2**:455, 1877-1880.

22. Blackfan: Acute Nephritis in Children with Special Reference to the Treatment of Uremia, Bull. Johns Hopkins Hosp. **39**:69 (Aug.) 1926.

extreme anasarca of the skin. It has been claimed by Volhard [5] and by others that failure to find edema of the brain at necropsy does not necessarily mean that it was absent during life. If this is so, it seems difficult to see why the edema should disappear in some cases and remain in others, and it must be concluded that failure to find edema of the brain at necropsy is strong evidence that it was not present in marked degree during life.

It is not clear how cerebral edema, when present, is produced. Of course, the mechanism suggested by Traube [12] is untenable, for we now know that most of the patients do not have hydremia. Moreover, arterial hypertension does not by any means necessarily indicate capillary hypertension and therefore would not be effective in forcing fluid from the capillaries. The cerebral edema in these cases is not merely part of a general edema, for the most widespread edema may be present (as in nephritis) without any cerebral edema, and conversely the cerebral edema may be marked without any edema elsewhere, as we have seen in eclampsia gravidarum. Volhard [5] believed that cerebral edema in the hypertensive encephalopathy is due to ischemic injury of the capillaries of the brain resulting from arteriolar constriction. There can be little doubt that the cerebral edema in these cases is the result of the phenomena producing the hypertension, for it occurs only in the presence of the latter, but we do not know the precise nature of the relationship. We are unable to agree with Blackfan's view that the edema of the brain causes, through medullary compression, the rise in blood pressure, for the latter is present before the onset of the cerebral symptoms and even the "extra rise" preceding the cerebral attack may come on gradually during a week or more, as was illustrated several times in the foregoing case. It is hard to conceive of the cerebral edema as producing through medullary compression an elevation of blood pressure as its sole symptom.

The group of symptoms here termed the hypertensive encephalopathy was subdivided by Volhard [5] in his original description into two pathogenetically distinct parts, acute and chronic false uremia. In acute false uremia, he considered the symptoms due to cerebral edema; in chronic false uremia, to cerebral angiospasms. We do not believe that such a division can be carried out, for the primary pathogenetic factor in all the cases is the cerebral anemia resulting from arteriolar constriction, the edema being one of the consequences of the ischemia. In turn, the edema also produces symptoms in some cases, but this is secondary. The attacks which come and go as quickly as did the individual seizures in the case described are evidently the direct results of the cerebral vasoconstriction. However, we have seen that these attacks may be frequently repeated over a long period of time so as to give a "chronic" picture despite the fact that at no time is there evidence of edema of the

brain. As is well known from postmortem observations, a considerable degree of cerebral edema may be present without causing any symptoms, but in those cases of hypertensive encephalopathy in which the cerebral symptoms present for a considerable time a picture simulating that of tumor of the brain with severe headache, cerebral vomiting, perhaps convulsions or focal cerebral symptoms with a high pressure of the cerebrospinal fluid and well marked choked disks (in one of our cases more than 5 diopters), it is probable that there is marked edema of the brain. Such cases are seen particularly in the toxemia of pregnancy and in children with glomerulonephritis. However, moderate papilledema or increased pressure of the cerebrospinal fluid in themselves do not necessarily indicate edema of the brain in a hypertensive patient. The papilledema may be the initial phase of albuminuric retinitis, as is not at all uncommon, and may have no relation to increased intracranial tension. And it is not uncommon to find long continued moderate elevation of the subarachnoid pressure in hypertensive patients, though no other evidence of edema of the brain develops and none is found at necropsy.

There does not seem to be any convincing evidence that edema of the brain, in itself and in the absence of arterial hypertension, can produce the picture of the hypertensive encephalopathy in nephrosis. Volhard [5] mentioned a case said to have been observed by another, but does not seem to have seen one himself.

From all available evidence, the cerebral syndrome here called the hypertensive encephalopathy has as its essential cause arterial hypertension, edema of the brain being only inconstantly present as a result of the hypertension, though it may, when present, contribute essentially to the clinical picture. We do not know why the hypertensive encephalopathy complicates only certain varieties of hypertension—those found in glomerulonephritis, the toxemia of pregnancy and lead poisoning—but does not occur in so-called essential hypertension. It will be noted that the varieties of hypertension in which the hypertensive encephalopathy occurs are those in which the hypertension often arises, or is increased suddenly, while in essential hypertension the increased blood pressure usually sets in gradually. We do not know whether this difference is significant for the pathogenesis of the hypertensive encephalopathy. The mechanism of the cerebral vasoconstriction in these cases is as dark as that of the hypertension itself. Vaquez [8] believed the vasoconstriction to be due to epinephrine, but this is no more proved than his epinephrine theory of hypertension. In the cases of lead poisoning, the vascular contraction is presumably due to the action of the lead on the vessels, and in the toxemia of pregnancy to the hypothetical

eclampsia toxin. Foster [23] claimed to have isolated a crystalline base that produces convulsions from the blood of nephritic patients with convulsions, but this interesting investigation, so far as we know, has never been confirmed. The genesis of the cerebral vasoconstriction, like that of the antecedent vasoconstriction, must as yet be considered as completely unexplained.

That cerebral anemia can produce epileptiform convulsions has been known since the classic experiments of Kussmaul and Tenner.[24] They were able to produce immediate epilepiform convulsions in the rabbit by ligating the arteries to the head. Immediately after the ligature was released, the convulsions ceased. Recently, it has been shown by Dandy [25] that clonic convulsions can be produced only by stimulating the motor cortex, and no other cortical or subcortical regions; consequently, the motor cortex must be involved in the cases showing epileptiform convulsions.

SUMMARY

The acute cerebral episodes of diffuse glomerulonephritis, the toxemia of pregnancy and acute lead poisoning are symptomatically identical, consisting of such symptoms as epileptiform convulsions, coma, violent headache, cerebral vomiting and such focal cerebral symptoms as aphasia, amaurosis and hemiplegia.

These cerebral episodes occur only in patients with arterial hypertension and are generally preceded by an additional rise in blood pressure above the previous high level. For this reason, the term hypertensive encephalopathy is proposed for the acute cerebral episodes occurring in hypertensive states.

The hypertensive encephalopathy is not the result of impaired renal function, so the term acute uremia is a misnomer.

Available evidence indicates strongly that the hypertensive encephalopathy is the result of cerebral anemia produced by cerebral vasoconstriction. The cerebral edema which is present in some, but not in all, of the cases is secondary to the vasoconstriction, though the exact mechanism of the connection is not clear. While the cerebral edema produces symptoms in some cases, it is not the essential cause of the hypertensive encephalopathy.

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23. Foster: Uremia, Harvey Lectures **16**:52, 1920-1921.

24. Kussmaul and Tenner: Epileptiform Convulsions from Hemorrhage, New Sydenham Society, London, 1859.

25. Dandy: Experimental Investigation of Convulsions, J. A. M. A. **88**:90 (Jan. 8) 1927.

A case of recurrent hypertensive encephalopathy is described in which the cerebral episodes were repeated many times and in varying forms over a period of twenty months.

Generalized convulsions are rarely a symptom of true uremia, having occurred in only two of fifty-one cases of chronic interstitial nephritis showing nitrogen retention.

INFLUENCE OF POSTURE ON PHENOLSULPHONPHTHALEIN TEST FOR KIDNEY FUNCTION *

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Studies on the so-called functional albuminuria, also variously designated as cyclic, intermittent, physiologic, orthostatic, etc., first focused attention on posture as a factor in renal activity. Naturally, the criterion most often used in the earlier works on this subject was the appearance of albumin in the urine. The volume of urine excreted in different body postures had been recorded by some investigators only as subsidiary observations. Edel [1] noted decreased urine volume during the standing posture coincident with the maximum albuminuria and, conversely, an increased volume on the assuming of a recumbent posture when albumin disappeared from the urine. Linnoisier and Lemoine [2] studied the influence of posture on renal activity by making twelve hour observations on renal and albuminuric patients. Notwithstanding the lack of adequate control of diet and water intake, they could observe a definite decrease, not only of the urine, but of urea and chlorides, during standing, as compared with the urine collected while the subjects were in bed. They also [3] found that the excretion of potassium iodide and of methylene blue was distinctly lowered when the patient was in the standing posture, and called attention to this factor in connection with the renal function tests in vogue at the time. These authors thought that the decreased secretion in the upright position was due to "torsion of the renal pedicle" brought about by a slight descent of the kidneys due to gravity. In support of this theory they point out [4] that in pregnant women a reverse relationship obtains; namely, increased renal activity on standing and decreased on lying down, the weight of the gravis uterus compressing kidney and pedicle more in the recumbent than in the erect position. Their data on this point are meager, and, as they themselves admit, this relationship is not constant.

Since the general adoption of the better and quicker method of testing renal function introduced by Rowntree and Geraghty,[5] little or no

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* From the Physiology Laboratory of the University of Chicago.

1. Edel: München med. Wchnschr. **48**:1833, 1901.
2. Linnoisier and Lemoine: Compt. rend. Soc. de biol. **55**:466, 1903.
3. Linnoisier and Lemoine: Compt rend. Soc. de biol. **55**:605, 1903.
4. Linnoisier and Lemoine: Compt. rend. Soc. de biol. **58**:691, 1903.
5. Rowntree and Geraghty: J. Pharmacol. & Exper. Therap. **1**:579, 1910.

attention has been given to posture as a possible modifying factor. In 1916 Barker and Smith [6] reported phenolsulphonphthalein tests on six patients with orthostatic albuminuria, but were able to test the influence of posture on only two of them. One patient (case 1) showed a distinct increased phenolsulphonphthalein excretion in the recumbent posture over that in the upright position. The other patient (case 6) did not show any change. Norgaard,[7] using a modification of the Strauss water test in twelve cases of orthostatic albuminuria found much reduced elimination of water and chloride during four hours of standing as compared with the elimination in similar periods of recumbency.

While considerable work has been done on patients with orthostatic albuminuria, little has been done to test the influence of changes of posture in renal activity on normal persons. Recently, White, Rosen, et al.,[8] in a series of well controlled experiments on normal persons, proved conclusively that renal activity, as a whole, is increased in the recumbent posture as judged by the greater elimination of water and solids, except ammonia, when compared to that in standing.

The present studies were undertaken to determine the influence of posture on the phenolsulphonphthalein renal function test to see whether such an influence manifests itself, and if so, to what extent in normal persons. It was felt that such data would be useful in interpreting the results in pathologic cases and might suggest new aids to differential diagnosis.

PROCEDURE

The experiments were made on two healthy laboratory workers, with neither symptoms nor previous history of impaired kidney function. The intake of food and water on the night preceding the experiment was not rigidly controlled save for the usual habits of the person. On the following morning, however, the subjects partook of a standard breakfast which excluded tea, coffee and water.

The tests were carried out as follows: 1 cc. of a solution containing 6 mg. of phenolsulphonphthalein was injected subcutaneously. The bladder was emptied; a definite quantity of water was taken by mouth, and the subject was made to lie quietly in bed for two hours. During this period hourly samples of urine were collected, their volumes were measured and the amount of dye eliminated was determined colorimetrically in the usual way. At the end of the two hours a second subcutaneous injection of the same amount of dye was administered; the same quantity of water was drunk, and the subject changed to the standing position for another two hours, avoiding muscular exertion as much as possible. Samples of urine were collected hourly and examined as before. Or, conversely with the same general procedure, the subject started the experiment in the standing posture and ended in the recumbent. Most of the control procedures were carried out in essentially the same manner as the fore-

6. Barker and Smith: Am. J. M. Sc. **151**:44, 1916.
7. Norgaard: Acta med. Scandinav. **8**:304, 1923.
8. White, Rosen et al.: Am. J. Physiol. **78**:185, 1926.

going except that instead of the posture being changed during the last two hours the subject continued in the same posture he started with. A few control experiments were carried out along these same lines but with only one subcutaneous injection of 6 mg. of the dye. This type of control was subsequently abandoned as being of little value for the purpose in view.

At first, the intake of water during the experiment was fixed at 200 cc. per two hours, taken immediately after the injection of the dye. Due to the difficulty experienced by one subject (M. H. F.) in voiding small quantities of urine, it was decided to increase the water intake in both subjects and to give the water in two doses. As a result, M. H. F., the larger of the two, received in the later experiments 300 cc. at the time of injection, and 200 cc. at the beginning of the second hour of each two hour period. Similarly, N. C. received 200 cc. and 100 cc. for each two hour period. In this manner we could assure a fairly uniform diuresis throughout the two successive two hour periods, without gastric discomfort.

From time to time the urines were tested for albumin. One subject, N. C., was able to urinate every thirty seconds. In this person the first appearance of the dye in the urine was observed from time to time. From the constantly negative albumin tests and the unchanged first appearance time of the dye, together with the complete absence of any abnormal subjective feelings we feel reasonably certain that our results were obtained from kidneys that remained normal throughout the rather long series of injections.

RESULTS

Table 1 represents the results on N. C. and M. H. F., grouped according to the type of procedure followed:

Group A, R_1S_2
Group B, S_1R_2
Group C, R_1R_2
Group D, S_1S_2
} = two injections, one at the start; another after two hours

Group E, R_1R_2
Group F, S_1S_2
} Only one initial injection

R stands for recumbent, *S*, for standing. The number following the letter indicates: 1, the first two hours; 2, the last two hours. All the figures for excretion are totals for two hour periods.

For convenience of expression the 6 mg. of phenolsulphonphthalein injected has been designated 100 units. This enables us to distinguish the actual quantity excreted from the percentage elimination, especially in dealing with the percentage elimination of the last two hours, in which we have to reckon with a residue from the previous two hour period. There is no way of estimating accurately the amount of this residue. A certain portion of the dye is excreted through other channels, and some may be destroyed in the body. These are, however, relatively small quantities for two hours, compared with that eliminated through the kidneys. By subtracting the elimination of the first two hours from the 100 units injected at the start, we get a figure which is our closest approach to the quantity of this residue. The number of

TABLE 1.—*Results of Tests to Determine Influence of Posture on Renal Function*

EXPERIMENTS ON N. C.

	Exp.	Recumbent first 2 hours (R_1) Dye: Elimination per Cent	Water Cc.: Intake	Water Cc.: Output	Standing last two hours (S_1) Dye: Units in Body *	Dye: Elimination per Cent	Water Cc.: Intake	Water Cc.: Output
	1	66.1	200	73	133.9	43.2	200	79
	2	74.4	200	350	125.6	38.1	200	232
	21	44.0	300	373	156.0	39.2	300	372
A	25	71.4	300	353	128.6	41.4	300	282
	29	43.4	300	452	156.8	37.8	300	310
	48	61.9	300	241	138.1	51.1	300	341
	52	62.7	300	480	137.3	56.8	300	309
		Standing first 2 hours (S_1)			Recumbent last 2 hours (R_1)			
	3	43.7	200	125	156.3	50.2	200	576
	4	46.6	200	155	153.4	39.5	200	369
	23	44.0	300	207	156.0	46.4	300	752
B	27	40.0	300	69	160.0	46.3	300	491
	38	51.5	300	89	148.5	54.3	300	490
	46	47.1	300	157	152.9	58.7	300	555
	54	52.0	300	48	148.0	62.3	300	675
		Recumbent first 2 hours (R_1)			Recumbent last 2 hours (R_2)			
	33	60.7	300	205	139.3	49.2	300	731
	36	56.4	300	210	143.6	53.9	300	712
C	42	55.2	300	265	144.8	53.9	300	751
	50	57.5	300	168	142.5	49.4	300	750
		Standing first 2 hours (S_1)			Standing last two hours (S_2)			
	30	46.0	300	117	154.0	47.8	300	392
	31	45.0	300	118	155.0	40.0	300	392
D	40	57.9	300	172	142.1	52.1	200	210
	44	57.1	300	160	142.9	54.7	300	463
	56	63.6	none	93	136.4	62.9	none	60
		Recumbent first 2 hours (R_1)			Recumbent last 2 hours (R_2)			
	11	32.7	500	604	67.3	23.9	150	590
E	13	34.1	500	580	65.9	18.5	200	670
	16	51.3	500	539	48.7	39.9	200	581
		Standing first 2 hours (S_1)			Standing last two hours (S_2)			
	9	49.3	500	228	50.7	21.3	200	311
F	14	53.9	300	65	46.1	35.7	300	233
	18	56.2	500	282	43.8	26.7	200	266

EXPERIMENTS ON M. H. F.

	Exp.	Recumbent first 2 hours (R_1) Dye: Elimination per Cent	Water Cc.: Intake	Water Cc.: Output	Standing last two hours (S_2) Dye: Units in Body *	Dye: Elimination per Cent	Water Cc.: Intake	Water Cc.: Output
	5	78.9	400	517	121.1	60.0	400	115
	7	59.3	400	515	140.7	41.2	400	106
	24	66.8	500	524	133.2	57.9	500	210
A	28	93.0	500	560	107.0	69.2	500	168
	39	65.4	500	585	134.6	44.8	500	233
	47	63.9	500	572	136.1	61.2	500	236
	55	71.1	500	540	128.9	60.7	500	128
		Standing first 2 hours (S_1)			Recumbent last 2 hours (R_2)			
	6	48.5	400	271	151.5	44.1	400	868
	8	47.0	400	245	159.3	50.7	400	580
	22	86.0	500	125	114.0	71.1	500	910
B	26	72.9	500	117	127.1	56.6	500	921
	49	63.2	500	139	136.8	70.1	500	794
	53	62.9	500	115	137.1	61.9	500	694
	57	73.2	500	67	126.8	76.7	500	771
		Recumbent first 2 hours (R_1)			Recumbent last 2 hours (R_2)			
	32	64.9	500	434	135.1	66.0	500	801
C	35	63.1	500	456	136.9	59.3	500	763
	41	81.5	500	423	118.5	74.1	300	588
	45	67.9	500	890	132.1	60.5	500	611
		Standing first 2 hours (S_1)			Standing last two hours (S_2)			
	34	60.4	500	368	139.6	52.2	500	414
D	37	56.7	500	54	143.3	61.2	500	66
	43	70.3	500	110	129.7	70.8	500	484
	51	61.5	500	220	138.5	60.7	500	237
		Recumbent first 2 hours (R_1)			Recumbent last two hours (R_2)			
	12	57.7	700	547	42.3	30.9	200	317
E	15	74.4	700	443	25.6	30.4	400	668
	19	77.7	700	393	22.3	40.3	400	629
		Standing first 2 hours (S_1)			Standing last 2 hours (S_2)			
	10	47.7	700	220	52.3	32.3	400	197
F	17	67.5	700	438	32.5	59.0	400	179
	20	60.0	700	450	40.0	43.5	400	160

* These columns include the amount of dye left presumably from the previous injection plus the quantity given in the second injection, when this has been done. All figures for dye and water elimination are for two hour periods

units of this probable residue plus the 100 units injected at the beginning of the last two hour period gives the figures given under the column "units in body," from which the percentage elimination of the last two hours is calculated. Considering that the destruction of the dye in the body and the elimination through extrarenal channels are comparatively small, and that these factors operate in every case at equal periods of time, namely, two hours, we feel that our calculation of this residue, though not exact, is accurate enough for comparative purposes.

In spite of variations in individual figures, the results indicate a definite though not marked increase in dye elimination in the recumbent posture, amounting in two hours with the quantities used, to about 10 to 13 per cent of the excretion of the erect position. This tendency

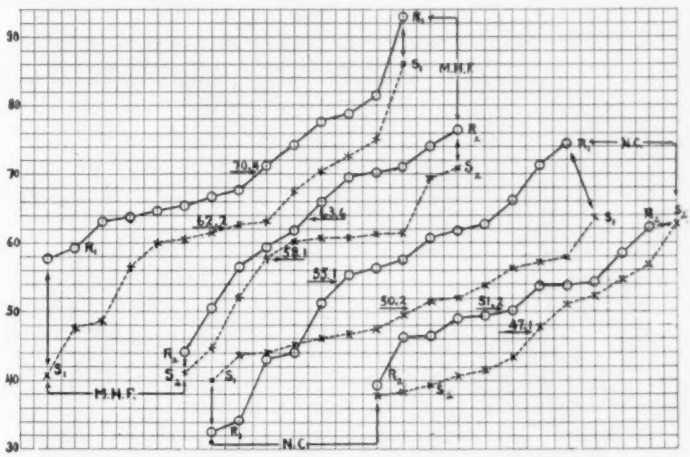

Fig. 1.—Influence of posture on phenolsulphonphthalein elimination. R_1 indicates recumbent first two hours; R_2, recumbent last two hours. S_1, standing first two hours; S_2, standing last two hours; ordinates, percentage elimination; abscissas, individual results arranged in order of increasing magnitude.

is manifest with the various criteria used in evaluating the results. More striking is the effect on the volume of urine of the recumbent posture, showing an increase of more than 100 per cent over that of the two hour standing period.

ANALYSIS OF DATA

Phenolsulphonphthalein Excretion.—Several ways of comparing the dye elimination (table 1) are possible.

1. Comparison of R_1, the two hour elimination following the first injection in the recumbent posture, with S_1, the two hour elimination

following the first injection in the erect posture, in the experiments of all groups.

2. Comparison of R_2, the percentage of elimination following the second injection in recumbency, with S_2, the percentage elimination following the second injection while standing, in the experiments of groups *A, B, C* and *D*.

Chart 1 represents graphically the foregoing comparisons for N. C. and M. H. F. The ordinates represent percentage elimination, and the abscissas, the individual results arranged in order of increasing magnitude. The elimination during the recumbent posture was distinctly higher than that during standing. Two extremely low recum-

TABLE 2.—*Comparison of Percentage Elimination During Successive Two Hour Periods on the Same Day* *

Subject	Group A $S_2—R_1$		Group C (Control) $R_2—R_1$	Group B $R_2—S_1$		Group D (Control) $S_2—S_1$
	—22.9		—11.5	+ 6.5		+1.8
	—36.3		— 2.5	— 7.1		—4.1
	— 4.8		— 1.3	+ 2.4		—5.8
N. C.	—30.0		— 8.1	+ 6.3		—2.4
	— 5.6		.....	+ 2.8		—0.7
	—10.8		.....	+11.6		.....
	— 5.9		.....	+10.3		.....
Mean	—16.6		— 5.8	+ 4.7		—2.2
Attributable to change of posture		—10.8			+6.9	
	—18.9		+ 1.1	— 4.4		—8.2
	—18.1		— 3.8	+10.0		+4.5
	— 8.9		— 7.4	—14.9		+0.5
M. H. F.	—23.8		+ 1.6	—16.3		—0.8
	—20.6		.....	+ 6.9		.....
	— 2.7		.....	— 1.0		.....
	—10.4		.....	+ 3.5		.....
Mean	—14.8		— 2.1	— 2.3		—1.0
Attributable to change of posture		—12.7			none	

* Taken from the experiments of groups A, B, C and D, table 1.
* The figures indicate how much more (+) or less (—) is the the excretion of the first two hour period than that of the second two hour period.

bent figures for N. C. fall distinctly below the lower limits of the standing elimination. The subject had a severe cold, slight headache and general malaise at the time of those tests. Similar low values were never again encountered in the whole series. These two results may thus be discarded. Yet, even including them in the series under the consideration, the average of the recumbent figures is distinctly higher. Chart 1 also brings out the fact that the percentage of excretion during the first two hours, as well as during the last two hours, was decidedly greater in M. H. F. than in N. C., a fact which will perhaps not be brought out by a few isolated tests. Likewise, the recumbent increase of elimination over the standing was greater in M. H. F.

3. Comparison of the four hour elimination in recumbency and standing following one injection of the dye. Groups *E* and *F*, which

fall under this category, indicate increased recumbent excretion for M. H. F. but not for N. C. In the latter case, however, two of the three recumbent tests are the exceptionally low values mentioned previously. For the experiments on N. C., therefore, this criterion is indecisive.

4. Comparison of the percentage of elimination during standing and during recumbency on the same day. From table 3 it is apparent that the dye elimination in the second of successive two hour periods was usually a little less than that of the first period, if the posture remained unchanged (experiments of groups *C* and *D*). When the posture was changed from the recumbent to the erect, the elimination during the second period was more markedly decreased. This was true in both N. C. and M. H. F. (experiments of group *A*). When, however, the change was made from the erect to the recumbent posture, only in

TABLE 3.—*Four Hour Output of Urine*

	Recumbent			Standing		
		Output, Cc.			Output, Cc.	
Subject	Intake, Cc.	Actual	per 100 Cc. Intake	Intake, Cc.	Actual	per 100 Cc. Intake
N. C.	600	936	156	600	509	85
	600	922	153	600	510	85
	600	1,016	169	500	382	76
	600	918	153	600	623	104
	650	1,194	183	700	539	77
	700	1,250	178	600	298	49
	700	1,120	160	700	548	78
M. H. F.	1,000	1,235	123	1,000	782	78
	1,000	1,219	122	1,000	120	12
	800	1,011	126	1,000	594	59
	1,000	1,501	150	1,000	457	46
	900	864	96	1,100	417	38
	1,100	1,111	101	1,100	617	56
	1,100	1,022	93	1,100	610	55

N. C. was there a definite increase in elimination. This will be referred to later.

Elimination of Water.—Water, unlike phenolsulphonphthalein, is necessary in the body economy and behaves like a threshold substance. Since body water balance is generally constant, water excretion is proportional to the intake, other things being equal, and for the relatively short periods of observation made in the present experiments, the elimination at any particular period was also influenced by the excretion of the previous periods. The room temperature did not vary more than 3 C. from day to day during the seven months covered by these experiments, so the variations in excretion of water through the kidneys due to this factor may be neglected.

1. Comparison of the output of the first two hours in one posture with that of the first two hours in another posture. Chart 2 represents such a comparison taken from all the groups of experiments in table 1. The ordinates give the volume of excretion per hundred cubic centi-

meters of intake, and the abscissas are the individual results arranged in order of magnitude. The increased volumes in recumbency are striking and consistent.

2. Comparison of the total output in the experiments of groups *C*, *D*, *E* and *F* in which one posture was kept for four hours. Recumbency increased the output from 50 to 200 per cent of the volume during standing, as may be readily seen from table 3.

3. Comparison of volumes of urine of two successive two hour periods on the same day. When one posture was maintained through the two successive periods, the urine volume of the second period was

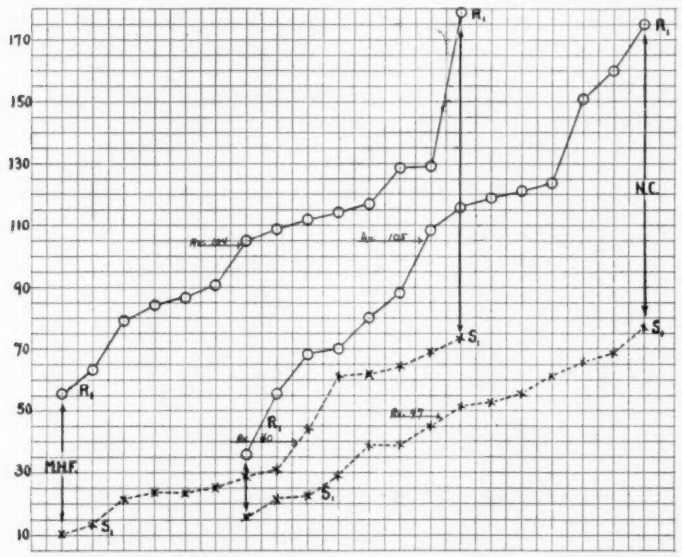

Fig. 2.—Influence of posture on urine output. R_1 indicates recumbent first two hours; S_1, standing first two hours; ordinates, volume per hundred cubic centimeters intake; abscissas, individual results arranged in order of increasing volumes.

a little greater than that of the first. A change from the recumbent to the erect posture effected a striking decrease in volume of urine (table 4). Conversely, a change from the erect to the prone position effects a significant increase in volume.

Volume of Urine and Excretion of Dye.—Rowntree and Geraghty [8] stated that the elimination of phenolsulphonphthalein was independent of the volume of output of urine. Snowden,[9] however, in 1921 reported

9. Snowden: Arch. Int. Med. **28**:603, 1921.

that for diseased kidneys the percentage of dye eliminated ran fairly parallel with the volume of the urine. Similarly, Lundsgaard and Moeller,[10] on patients with cardiac disease but no albuminuria, observed that with extremely low volumes of the urine the elimination of dye was also decreased.

Although such low volumes (10 cc. or less) as those reported by Lundsgaard and Moeller were never encountered by us, our data disclose absolutely no correlation between the volume of urine and the elimination of dye. It may be reasonable to assume that the damaged renal cells of nephritic patients are less able to work with small volumes than normal cells. Yet, it is difficult to disregard the possibility

TABLE 4.—*Comparison of Volumes of Urine Per Hundred Cubic Centimeters Intake of Two Successive Two Hour Periods on the Same Day* *

	Group A $S_2—R$	Group C (Control) $R_2—R_1$	Group B $R_2—S$	Group D (Control) $S_2—S_1$
	+ 3	+175	+225	+ 91
	−59	+167	+107	+ 91
	0	+162	+182	+ 48
N. C.	−24	+194	+141	+101
	−47	.....	+133	.....
	+34	.....	+133	.....
	−57	.....	+209	.....
Average	−21.5	+174.5	+147	+ 83
Effect of change to standing posture		−196	Effect of change to recumbency	+64
	−100	+ 73	+149	+10
	−103	+ 61	+ 84	+ 2
	− 63	+112	+157	+75
M. H. F.	− 78	− 56	+161	+ 3
	− 70	.....	+131	....
	− 67	.....	+116	....
	− 82	.....	+141	....
Average	− 80.5	+ 47.5	+134	+22.5
Effect of change to standing posture		−128.0	Effect of change to recumbency	+111.5

* The figures represent the increase (+) or decrease (−) in volume of the second two hour period as compared with that of the first two hour period. The subnumerals 1 and 2, following R or S, denote the first and second two hour periods respectively.

that the conditions giving rise to reduced excretion of dye concomitantly cause reduction of volume of output, and that the reduced volume and excretion of dye, though often coexistent, do not necessarily depend on each other unless extremely low volumes are encountered.

Demerits of the Subcutaneous Injection.—The current practice in the application of the phenolsulphonphthalein test for renal function is to employ the intravenous route. Unquestionably when this method is followed one variable is eliminated. In fact when we examine the data on the use of the intravenous method we are struck at once, not only by the uniformity, but by the higher percentages of the elimination of the first hour. While these data have remained more or less unchallenged, the following facts have been generally overlooked.

10. Lundsgaard and Moeller: Acta med. Scandinav. **63**:242, 1926.

Most of the data purporting to show the advantages of the intravenous route consist of one test on different persons, and emphasize especially the first hour elimination. There are only a few instances in which more than three or four tests have been made on the same person, either by the subcutaneous or by the intravenous route alone.

By arranging our data in chronological order we noted several groups of from two to five successive experiments in which the two hour excretion of dye was remarkably constant, being well within a variation of 10 per cent. It is possible that the five or six experiments on the same person which are offered as evidence of the reliability of the intravenous route are such a group as we have encountered; especially if the series of experiments is done within a short interval, when the circulation, diet, water intake and general body condition are fairly constant. Certainly, so few experiments do not permit a statement as to the reliability of any particular technic.

Sugimura and Aomura [11] studied the excretion of phenolsulphonphthalein on twenty-four healthy subjects, using different routes of

TABLE 5.—*Taken from Sugimura and Aomura*

Mode of Injection	Two Hour Percentage Excretion		
	Highest	Lowest	Mean
Subcutaneous	68.4	39.0	58.4
Intramuscular	79.8	44.0	64.2
Intravenous (with water intake)	84.7	43.0	72.6
(without water intake)	79.3	43.0	68.2

injection on each. From table 4 of their paper we calculated the two hour excretions with the different methods of injection used and found the following:

Sugimura and Aomura point out the advantages of the intravenous route in the following terms: "Die Ausscheidung Kurve erreicht dabei schon in der ersten halten Stunde ihren Kulminationspunkt um in der zweiten halben Stunde wieder steil abzufallen. Bei subkutaner und intramusculärer Injektion zeigen sich die Kurven als mehr inkonstant." In other words, emphasis is again given to the first hour. From the foregoing recalculated two hour table, the higher values for intravenous injection are evident, but it is also clear that as to the question of variability, one method of injection shows as much lack of uniformity as another.

Apparently, then, when the two hour excretions are taken into account the subcutaneous method of administration is not consistently more variable than the other methods. The multiplicity of factors capable of affecting the results makes one or two tests of little value in

11. Sugimura and Aomura: Iohoku J. Exper. Med. **7**:125, 1926.

medical cases. The subcutaneous route will permit as many determinations as necessary on the same patient, provided edema is not present. Our data, we believe, adds one more evidence to the already well known harmlessness of phenolsulphonphthalein, even with prolonged use. Furthermore, there is no evidence of development of any form of increased storage or increased destruction in the body.

INTERPRETATION

The variability of results even on the same subjects will always detract from the value of any small series of experiments of this nature. But our analysis of twenty-eight experiments on each of two subjects convinces us that there is a definite though not marked increase of from 10 to 13 per cent in the two hour elimination of phenolsulphonphthalein in the recumbent position as compared with that in standing. Our belief is strengthened, furthermore, by the fact that the degree of difference is always greater in M. H. F. than in N. C. with the various criteria used in evaluating the results. If the data are reliable enough in revealing a definite and constant individual difference, it follows that the definite and constant difference between standing and recumbency must be quite real.

Lundsgaard and Moeller,[10] in considering the extrarenal factors influencing the elimination of phenolsulphonphthalein, are led to believe that the excretion of this dye depends on the local circulation in the kidneys, which may be influenced by conditions affecting the general circulation, and that consequently the phenolsulphonphthalein test is "of considerable value as an early and frequently occurring sign of circulatory insufficiency." White and his co-workers [8] discuss at length the probable causes of the postural effects on renal activity. The kidney vessels, perhaps, participate in the general body relaxation accompanying rest in bed. Regardless of the mechanism of urine formation the caliber of the local blood vessels must be an important factor. With a large capillary bed, other things being equal, there will be a greater filtration and a greater local circulation rate, although the two need not be coexistent, as indicated by the fact that water, pre-eminently dependent on filtration for its formation, may be increased while dye excretion is low; or decreased, with a high rate of excretion of dye. That the local circulation rate is increased in recumbency is made the more probable by the fact that the general circulation rate is greater in recumbency, as shown by Field and Bock,[12] Rosen and White,[13] Turner [14] and others. Abundant experimental data have accumulated to support the view that

12. Field and Bock: J. Clin. Investigation **2**:67, 1925.
13. Rosen and White: Am. J. Physiol. **78**:158, 1926.
14. Turner: Am. J. Physiol. **80**:601, 1927.

the local blood supply to the kidneys is strongly controlled by nervous influences. If the influence of recumbency depends on the state of relaxation of the local blood supply, then it must in large measure depend also on nervous influences. That this might be so is indicated by the fact that, whereas, in changing from recumbent to standing the difference in elimination due to posture is clear, in changing from standing to recumbent, it is less clear. This fact may be interpreted to mean that in the early morning hours, coming from home to the laboratory, the body is still in low nervous tension from the previous night's rest. Hence, when the recumbent posture is assumed first, relaxation is easier When, however, the recumbent posture is assumed after two hours' standing, relaxation is not so easily obtained. From table 2 it is easy to see that the difference in dye excretion attributable to posture is greater in changing from recumbent to standing than in making the reverse change. Furthermore, in M. H. F. no difference could be attributed to the posture in changing from standing to recumbent. This subject was of a high strung nervous constitution, and his power of voluntary relaxation was not good, as shown during metabolism tests done on him in connection with some other work, and also by his difficulty of voiding small volumes of urine.

It will be interesting to determine to what extent posture influences renal activity in those with cardiorenal disorders. Will posture influence kidney function more in predominantly cardiac disorders than in predominantly renal conditions? Might the posture effect on the excretion of dye and water considered separately give a clue for differential diagnosis? It is hoped that these problems will be worked out by experimenters who can command proper facilities for further investigation.

As a result of the foregoing studies and the possibilities mentioned, it seems essential that renal function tests should be made with the patients in recumbent posture to eliminate one more variable, especially in borderline cases. It might be advisable, furthermore, to give water in fractional doses, with a view to assuring at the time of collection of the sample, a volume large enough to stimulate micturition even in nervous subjects, and yet small enough to exclude the possibility of renal inhibition by bladder distention.

SUMMARY AND CONCLUSIONS

1. The elimination of phenolsulphonphthalein in normal persons is greater in the recumbent posture than during standing. The difference (from 10 to 13 per cent) though definite is not marked, but should be taken into account in making phenolsulphonphthalein tests in borderline cases. The possibility that the difference might be greater in cardiorenal disorders is pointed out.

2. The effect of recumbency in increasing the volume of output is marked (from 50 to 200 per cent), confirming the results of the earlier investigators.

3. The probable causes of these postural effects are discussed.

4. On the basis of fifty-seven experiments on two subjects, at intervals of at least five days, it is shown that the hypodermic route is not as unreliable as is generally believed when the two hour eliminations are taken into account.

5. The absence of toxic effects during the eight months covered in these studies is offered as one more evidence of the harmlessness of phenolsulphonphthalein. There is no evidence of the development of any increased storage or increased destruction in the body during this frequent and long continued use.

6. Slight modifications in the technic of renal function tests are suggested.

Book Reviews

CLINICAL PHYSIOLOGY IN RELATION TO MODERN DIAGNOSIS AND TREATMENT. By ROBERT JOHN STEWART MCDOWELL, D.Sc., M.B., C.R.C.P. (EDIN.), Professor of Physiology, King's College, University of London. Price, $7. Pp. 383, including an index, and a bibliography of six pages of recent books and monographs. New York: D. Appleton & Company, 1927.

According to the author, the book is intended for senior medical students and practitioners of medicine whose busy lives do not permit them to read more extensive textbooks. The author, thus, assumes on the part of the readers the knowledge secured in a thorough course in the fundamentals of physiology, and on the basis of this he endeavors to analyze or explain symptoms of disordered functions in patients.

This is not the first nor the ablest venture in this field. The informed reader finishes the book with the feeling that Professor McDowell has not materially improved on Hewlett's "Pathological Physiology," and in many chapters he is clearly inferior to the latter. On the whole the Professor McDowell shows less critical judgment in the handling of conflicting data than the late Professor Hewlett.

In speaking of medical students, the author says that "it is extremely difficult, indeed almost impossible from the study of ordinary textbook physiology, for him to see why a cardinal symptom of cardiac disease should be breathlessness." One may assume that today the student in every up-to-date medical school is given more than textbook physiology. A senior medical student who is nonplussed by seeing dyspnea in a patient with marked cardiac impairment either does not know his physiology or he has not learned to think.

The chapters on "Psycho-therapeusis" and on "Balance of the Endocrine Organs" seem particularly weak and speculative. We have a puff for a much advertised book selling scheme in the following sentence: "A system of memory training such as Pelmanism, is efficacious in that it forms associations of value around certain words." One is assured that "psychology is a true science." It would be nearer the truth to say that the best psychologists are working earnestly to make psychology a science. The chapter on "Endocrine Balance" is filled with vague statements such as the following: "The pituitary body (anterior lobe) is specially related to the structural adaptation of the body to its physical environment." "The posterior lobe of the pituitary is concerned with the adaptation of the body processes necessary in the continuation of the species." The following appears as bald statements of proven facts: "Both these glands (thyroid, pituitary) become atrophied in contraction." "The thyroid and pituitary are normally antagonistic to the pancreas." "The sympathetic is associated with activity or ketabolism, and the parasympathetic with anabolism." The author speaks of "the clinical phenomenon of growth," referring not to cancer, hyperplasia or wound healing, but to normal growth processes. He says that in pernicious anemia with a red cell count of 600,000 the general condition of the patient, provided he is resting, is quite good."

The up-to-date medical practitioner and the senior medical student in any first class school will reap meager profit in reading this volume. Even simple and well established facts are often obscured by the author's befuddled diction or attempts at philosophic abstraction. For example: "Breathing is the movement made by the body to maintain pulmonary ventilation. As such it may be considered the external expression of the body for the need of oxygen. . ." Platitudes like the following, are not rare: "A child whose diet is deficient cannot be expected to grow and the general ignorance in such matters is truly appalling."

As stated in the preface, the author starts for an ambitious albeit difficult goal, but at no point reaches the advanced posts already attained by the best books in normal and pathologic physiology.

DAS VERSAGEN DES KREISLAUFES. DYNAMISCHE UND ENERGETISCHE URSACHEN. VON PROF. DR. HANS EPPINGER, Direktor der Medizinischen Universitätsklinik in Freiburg, I, Br. DR. FRANZ KISCH and DR. HEINRICH SCHWARZ. Price, R. M. 16.50. Pp. 238, with 56 illustrations. Berlin: Julius Springer, 1927.

This monograph is an excellent attempt to analyze and explain the deficient physiology of patients with cardiac lesions (valvular and myocardic) in the light of recent physiologic researches on circulation, on blood, and on muscle physiology, notably those of Henderson, Hill, Meyerhof, Barcroft and others. The monograph contains, in addition, a good deal of experimental work on patients by the authors themselves. Most of these experiments deal with the oxygen required in rest and under measured work by patients with cardiac deficiency as compared to normal human beings. The report in the majority of such patients is higher oxygen requirement during rest and a much higher oxygen requirement during work as compared to normal men. The authors endeavor to explain this deficiency by an upset in the lactic acid metabolism in the body muscles due to more or less chronic asphyxia.

The monograph deals with the following main topics in the six chapters: The velocity of the blood flow as a measure of the peripheral circulation; the influence of physical work on circulation and on metabolism in patients with cardiac disease; the influence of physical work on lactic acid metabolism in cardiac deficiency patients; the significance of buffer processes for the circulation; experimental carbon dioxide poisoning, and, lastly, the theory of cardiac deficiency. The authors reach the conclusion that patients with cardiac deficiency produced more lactic acid than normal persons, and that there is developed in the former a deficiency in reconversion of lactic acid back to glycogen. In consequence of this there is an upset of blood neutrality in the direction of acidosis which in turn gradually causes impairment of the cardiac motor tissue.

The monograph reveals much thought and much able and conscientious experimentation. The conclusions are generally tentative and conservative. Only two criticisms may be directed against the volume, namely, many of the patients with cardiac deficiency recorded in the monograph probably had other pathologic processes besides the cardiac condition, so that before final conclusions can be reached similar experiments must be done on animals where one can be sure that the initial lesion at least is only that of the heart. There is also some carelessness in presentating the graphic data on many of the charts. Thus, for example, the date and the name of the patient is given without naming the particular disease. This is confusing as the reader must refer to various pages of the book to find the particular ailment from which the patient suffered. The authors also did not seem to be familiar with the fact that thyrotoxic patients require a high oxygen intake on doing physical work as compared to normal man. This fact was definitely established a number of years ago. But, as a whole the monograph is a distinct contribution to an interesting and difficult field of internal medicine.

SCIENTIFIC REPORTS OF THE GOVERNMENT INSTITUTE FOR INFECTIOUS DISEASES, vol. 5. The Imperial University. Tokio: Shirokane-Daimachi, Shibaku, 1926.

The director of the Institute, Nagayo, although this volume contains none of his own contributions, has good reason to be proud of the work of his associates. The 650 pages are replete with interesting reports of experimental work which comes up to a high standard.

The section on biology contains a series of studies by Miyagawa (the editor of the volume and his assistants) on the effect of injections of autolysates

of various organs. Injections of such materials invariably cause profound degenerative changes in the corresponding organ. An adequate explanation is not vouchsafed for this unusual phenomenon.

The most striking feature of the volume, however, is the article by W. Nakahara on the filtrable virus of the Rous chiken sarcoma. By a well planned series of investigations, he has shown beyond a doubt that the so-called "causative agent" actually does contain live sarcoma cells. By staining methods he first showed that this "causative agent" still contained apparently viable sarcoma cells after drying glycerination and passage through the Berkefeld filter. This fact is proved beyond a doubt by methods of tissue culture, so that the question can be considered as positively settled.

MODERN PRACTICE OF PEDIATRICS. By WILLIAM PALMER LUCAS. Price, $8.50. Pp. 962. New York: The Macmillan Company, 1927.

In this small volume of about 900 pages Dr. Lucas, with characteristic, unconventional scholarliness and scientific vigor, has brought the subject of pediatrics up to the immediate present. So true is this that even the well informed pediatrician, as well as the general practitioner and the advanced student, will find in it a constant source of reference for nearly all that is new in pediatrics. Especially valuable are the introductory chapters with their modern prophylactic note and the chapters on the blood and the diseases of the blood, on which the author speaks with well recognized authority. What the book lacks from the fact that no one man can any longer speak with final authority on all subjects pertaining to pediatrics is largely compensated by the vigorous and unconventional individuality of the author's presentation. In spite of the smallness of the book which carries with it the inevitable result that some subjects are treated too briefly to be of optimum service to the practitioner and the student, it can be warmly commended as a most valuable exposition of the modern Practice of Pediatrics.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOLUME II. ADMINISTRATION AMERICAN EXPEDITIONARY FORCE. Price, $3.40. Pp. 1123. Washington, D. C.: Government Printing Office, 1927.

This volume, like its predecessors, is prepared with the greatest attention to detail. It is well indexed so that any particular topic can be easily found.

The first twenty chapters are devoted to the organization of the various subdepartments in the Surgeon General's Office; the next few chapters to various types of hospitals and the two chapters following on evacuation of patients to the United States. The final section is on medical departmental activities of the American Forces in France.

The volume is profusely illustrated with carefully prepared charts, maps and other figures.